Global Health (IHCAR)
Department of Public Health Sciences
Karolinska Institutet, 171 77, Stockholm, Sweden

Uptake, adherence and discontinuation of antiretroviral treatment in the Kibera slum, Nairobi, Kenya

Christian Unge

Karolinska Institutet

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ABSTRACT

Background: As antiretroviral treatment (ART) is being scaled-up, long-term success depends on high adherence to ART and retention in care. Rapid urbanization and growing slum populations present specific challenges for sustaining HIV-infected patients on ART.
Aim: To study determinants for low adherence to ART in an urban slum in sub-Saharan Africa and to explore factors related to drop-out from ART.
Methods: All studies were conducted at the Médecins Sans Frontières's (MSF) or at the African Medical Research Foundation's (AMREF) HIV clinics in the Kibera slum, Nairobi, Kenya. Study I: 26 patients eligible for ART at the MSF clinic who choose to not initiate ART were interviewed to understand underlying reasons. Study II: Patient records were reviewed to study access to ART during the violence in Kibera following the general elections in Kenya 2007/08. Study III: Adherence to ART and drop-out from the programme was analyzed retrospectively through review of 830 patient records. Study IV: 20 patients known to have dropped-out of ART to seek alternative care/cure, were interviewed about their reasons. Study V: A prospective cohort study of 800 patients to analyze dose-adherence to ART by creating an adherence index based on dosing, timing and special instructions and performing Cox-regression survival analysis to study time to drop-out.
Findings: Study I: The main reason for not accepting ART was fear of taking medication on an empty stomach due to lack of food. Study II: During post-election turbulence in January 2008, 42% of 447 scheduled appointments were missed compared to 14% in January 2007. Study III: 27% of ART patients had a mean adherence below 95%. No factor remained independently associated with low adherence. 29% dropped out more than 90 days after the last prescribed dose. Residence in Kibera was associated with drop-out. The probability of remaining on treatment was 0.83 at 6 months, 0.74 at 12 months and 0.65 at 24 months. Study IV: The most important reasons for dropping-out from ART related to religious beliefs and traditional medicine were: patients' firm belief that traditional medicine was more effective/had fewer side effects compared to biomedical medicine; faith, praying and religious practices to seek cure from HIV; negative attitudes from religious leaders; and; important personal trigger events. Study V: Among 800 patients, 11% were non-adherent at 6 months follow-up (dose-adherence<95%). Undisclosed HIV-status and living below the poverty limit were significant predictors of adherence <95%. Using the adherence index, also taking adherence to timing and special food instructions into account, 38% of patients were defined as non-adherent. Lack of treatment buddy and low education were significant risk factors. Almost 1 in 4 dropped-out from the ART programme for more than 90 days after the last prescribed dose. Cox regression analyses showed a significantly higher hazard ratio for people who lacked a treatment buddy for support.
Conclusion: Sustaining HIV patients on ART in high-risk and highly mobile settings such as urban slums is a major future challenge. The high proportion of patients dropping out from ART and being non-adherent must be addressed using context-specific solutions. It is important to invest more in poverty reduction strategies in general, but also to encourage an open, non-judgmental discussion between patients and providers around possible foreseen challenges to treatment maintenance e.g. food shortages, religion and traditional medicine, in order to strengthen uptake and adherence to ART and to reduce drop-out from ART, especially important in resource-poor settings where stigma, and poverty is prevalent.
Keywords: Africa, urban slum, uptake, adherence, drop-out, HIV, ART, traditional medicine, religion.

LIST OF PUBLICATIONS

I Unge C, Johansson A, Zachariah R, Some D, Van Engelgem I, Ekstrom AM. *Reasons for unsatisfactory acceptance of antiretroviral treatment in the urban Kibera slum, Kenya.* AIDS Care 2008,20:146-149.

II Unge C, Sodergard B, Thorson A, Ragnarsson A, Carter J, Ilako F, Waweru M, Ekstrom AM. *HIV treatment in times of civil strife: serious threats to antiretroviral drug access in the Kibera slum following the Kenyan elections.* AIDS 2008,22:1693-1694.

III Unge C, Sodergard B, Ekstrom AM, Carter J, Waweru M, Ilako F, Ragnarsson A, Thorson A. *Challenges for scaling up ART in a resource-limited setting: a retrospective study in Kibera, Kenya.* Journal Acquir Immune Defic Syndr 2009,50:397-402.

IV Unge C, Ragnarsson A, Ekstrom AM, Indalo D, Belita A, Carter J, Ilako I, Sodergard B. *The impact of traditional medicine and religion on discontinuation of ART in an urban informal settlement in Nairobi, Kenya*. Submitted.

V Unge C, Sodergard B, Marrone, G, Thorson A, Lukhwaro A, Carter J, Ilako J, Ekstrom AM. *Long-term adherence to antiretroviral treatment and program drop-out in a high-risk urban setting in sub-Saharan Africa. A prospective cohort study*. Accepted for publication in PLoS ONE.

The papers will be referred to by their Roman numerals.

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LIST OF ABBREVIATIONS

3TC	Lamivudine
AACTG	Adult Aids Clinical Trials Group
AIDS	Acquired Immune Deficiency Syndrome
AMREF	African Medical Research Foundation
ANC	Antenatal Care
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT/ ZDV	Zidovudine
BHP	Biomedical Health Provider
CD4	Cluster of differentiation 4 (White blood cells)
CHW	Community Health Worker
CI	Confidence Interval
CSA	Continuous Single-Interval Measure of Medication Availability
D4T	Stavudine
DCT	Diagnostic counselling and testing.
DOTS	Directly observed treatments
EVF	Efavirenz
FDC	Fixed dose combinations
FTC	Emtricitabine
GDP	Gross domestic product
HAART	Highly Active Anti-Retroviral Treatment
HBM	Health Belief Model
HIV	Human immunodeficiency virus
HSP	Health Staff Personal
IMR	Infant Mortality Rate
KANU	Kenya Africa National Union
KSH	Kenyan Shilling
LTFU	Loss to follow up
MCAR	Missing Completely At Random
MDG	Millennium Development Goals
MEMS	Medical Event Monitoring System
MoH	Ministry of Health
MMR	Maternal Mortality Ratio
MSF	Médecins Sans Frontières
MTCT	Mother-to-child transmission
NGO	Non-governmental organization
NNRTI	Non- nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
NVP	Nevirapine
OR	Odds Ratio
PEPFAR	US President's Emergency Plan for AIDS Relief
PI	Protease Inhibitor
PLHIV	Person Living with HIV
PMTCT	Prevention Mother-To-Child Transmission

RRA	Rapid Result Approach
RRI	Rapid Result Initiative
RT	Reverse transcriptase
SSA	Sub-Saharan Africa
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
THP	Traditional Health Provider
UN	United Nations
US$	US Dollars
VCT	Voluntary counselling and testing
WHO	World Health Organization

PREFACE

When studying medicine at Karolinska Institutet I attended one of Professor Hans Rosling's lectures on global health. When leaving the lecture hall I knew how to begin my medical career: I wanted to work for Médecins Sans Frontières (MSF), the organization that he helped to establish in Sweden in 1993. I saw the possibility to combine my urge to explore the world with my profession as a medical doctor. So, in 2002, I realized this dream and went on a six-month mission for MSF in Burundi as the only medical doctor at a 140 bed hospital. Many of the patients suffered from "Disease X", for which there was no available treatment. Everybody on the staff knew that it was AIDS the patients were dying from but the Ministry of Health had not started any national HIV programmes and MSF had to follow the national policy. My frustration grew.

Later on when doing minor research projects at the Division of Global Health (IHCAR) I came to know my future supervisor, Anna Mia Ekström, who, at the time, had started a research team focusing on HIV/AIDS in low income countries. One of her research partners was the African Medical Research Foundation (AMREF), active in the Kibera slum, Nairobi, Kenya. At the same time I had been approached by the MSF research department in Brussels who had faced a clinical problem in the field: the HIV-infected patients who needed antiretroviral treatment in one of their clinics, in the Kibera slum, did not show up for treatment. MSF wanted to find out why.

At the time I did not know much about HIV, but when preparing for the MSF interviews in Kibera I started to realize to what extent the HIV epidemic has changed the lives of millions, in many different ways, especially in those African countries where whole generations were lost in the earlier phases of the epidemic. Both industrialized and developing countries are fighting the same virus but with totally different means. Never before in history have researchers and governments around the world spent so much money on one single disease. Much has been achieved, but the complexity of implementing HIV-treatment on the ground in weak, resource-poor, health systems, is still a major challenge.

Twenty five million people have died and every 15 seconds, another person is infected with HIV. This thesis aims to contribute to the development and implementation of more effective treatment programmes to benefit those who are infected.

BACKGROUND

THE HIV EPIDEMIC

In sub-Saharan Africa (SSA) AIDS is the leading cause of death [1]. Although only 12% of the world's population lives in SSA, this region accounts for 67% of all people living with HIV in the world and 72% of the whole world's AIDS-related deaths in 2008 [1]. The impact of the epidemic on many countries in SSA has been disastrous for the health care system, economy, business and for the individual patient in particular. In Swaziland e.g., one of the most affected countries in the world with an HIV prevalence of 26.1% (25.1%-27.1%), life expectancy has been halved from 1990 to 2007, from to 74 to 37 years [1].

Since the introduction of antiretroviral treatment (ART) in 1996, the peak of the epidemic seems to have been reached in 1996 when 3.5 million new infections (incidence) occurred globally compared to 2.5 million (i.e. a 30% decrease), twelve years later [1]. Today WHO estimates that 5.2 million people in the world have been initiated on ART [2]. This corresponds to a 10-fold increase in low- and middle-income countries only in the last five years [3]. Currently, about 42% of the people in need have been initiated on ART compared to a 7% global coverage in 2001 [1]. It takes between 9-11 years from being infected by HIV until AIDS symptoms appear if no treatment is initiated [1]. The peak of deaths in AIDS seems to have been passed in 2004, 8 years after introduction of ART, with 2.2 million AIDS-related deaths [1], slowly decreasing to 2 million in 2008. Some studies have shown a 95% decrease in HIV related mortality associated with ART [4].

A large part of the progress in reducing the incidence of HIV is the prevention of mother-to-child transmission (PMTCT) of HIV. From an estimated 30% to 35% risk of transmission without intervention, the risk for an infant to become infected by the mother is today 1% to 2% with antiretroviral prophylaxis and replacement feeding. These achievements in risk reduction come from optimal settings. In reality, many patients in SSA cannot practice exclusive breastfeeding and do not have access to enough information to follow all PMTCT recommendations. The global coverage of HIV pregnant women being reached by PMTCT services has increased from 10% in 2004 to 45% in 2008 [1]. PMTCT services are still insufficient with low access to ART services by pregnant women, shortages of obstetrical services and skilled personnel [1].

In SSA, 5-31% of married couples live in a sero-discordant relationship [5] and it has been estimated that 43% of all new HIV infections in adults are among people living in discordant relationships (2008) [6].

Many challenges persist in SSA, but in order to curb the HIV epidemic, preventive efforts must be strengthened and go hand in hand with treatment initiatives. The next chapter in the response to the HIV epidemic is to maintain people on ART and to sustain efficient and manageable HIV programmes.

Due to the continued stable incidence, rapid expansion of ART access and the resulting decrease in AIDS-related deaths, the number of people living with HIV is steadily increasing. This creates a growing challenge to the health systems, already sub-optimal in SSA, with shortages of skilled human resources for health and limited availability to second-line treatment [7-9].

Many people with HIV remain undiagnosed. In Kenya, an estimated 83% of the persons living with HIV (PLHIV) did not know their status in 2009 [10]. Children pose a specific challenge due to faster disease progression and most children die before their fifth birthday unless they receive ART[11].

Figure 1. *Map of Kenya*

Kenya at a glance

Kenya (Figure 1) became independent from the British in 1963 and has since then had three presidents. The first president, Jomo Kenyatta, was succeeded by Daniel Arap Moi in 1978. Kenya has a multi party system, but in reality the ruling party KANU (Kenya Africa National Union) has dominated the country under Kenyatta and Moi. The third and current president, Mwai Kibaki came to power in 2002 on an election campaign to fight corruption and to include all the different tribes from the country in the government. These promises have not yet been fulfilled and like his predecessors, Kibaki has appointed his fellow tribesmen (Kikuyus) to government positions.

The Kenyan economy is based on tourism and agriculture with tea being the primary export product. The population is 38 million with a population density of 47 per square kilometre. Kenya is a low income country with a gross domestic product per capita of 1200 US dollars [12]. Almost half, 46.6% of the households live below the poverty line [13] (Table 1).

Kenya has huge inequities regarding class, gender and region [14]. It is one of the ten most unequal countries in the world with a Gini-Coefficient of 0.57 (1=maximum inequality) while neighbouring countries like Uganda and Tanzania are much more equal (Gini-coefficients of 0.37 and 0.38, respectively) [14]. Ten percent of the population control more than 42% of the total economy [14]. In 2009, Kenya was ranked 146/180 on Transparency International's global corruption index, and Kenya has been struggling with corruption and bribery for many years [15]. On 5 August 2010, Kenya adapted a new constitution aiming at fighting corruption, among other things [16].

After the elections on 27 December 2007, Kenya was close to civil war. Mwai Kibaki was declared winner of the elections and the supporters of the opponent, Raila Odinga, claimed electoral manipulation, which was partly confirmed by international observers. The broken

promises of shared government in 2002 left many people frustrated and fuelled the violence after the elections in 2007 [17]. The main tribes involved in the post-election violence were the Kikuyus, Luos and Kalenjins. The most serious violence took place in the Nyanza province, Odinga's homeland, and in the Kibera slum of Nairobi, where all our studies in this thesis have been performed. Much of the initial violence was targeted against the Kikuyus [18]. After 59 days, a political compromise was achieved. One thousand five hundred people had been killed, 3 000 were raped and 300 000 were left internally displaced [17].

Health systems in Kenya

The United Nations ranks Kenya only as number 148 out of 177 countries in terms of Human Development achievements (based on literacy life expectancy, education and standard of living) [19]. Kenya is slow at achieving all millennium development goals (MDGs), and in particular the MDGs related to poverty and health due to a poor health system infrastructure, high corruption and weak institutions hindering not only effective drug supply and management systems, but also adequate human resource policies and higher quality health service provision [19, 20]. Health indicators have stagnated since the early 1990 because of a high and stable incidence of previously known diseases as well as the emergence of new diseases including HIV/AIDS, and a lack of adequate response from the health care sector [19]. There are also high variations in disease burden linked to gender, socio-economic factors and geographic regions within the country. Malaria is the most important cause of morbidity (30%) [19]. The incidence rates of mental illness and traffic accidents are increasing as the society develops while still struggling under the burden of poverty related diseases such as repeated breakouts of cholera due to contaminated water.

Kenya's health expenditure derives from three different sources: the government (29.3%), external donors (31%) and household expenditure (35.9%) [21].

HIV in Kenya

Basic data on the HIV epidemic are shown in Table 1. The HIV-prevalence in Kenya was 6.3% in 2008-9, but there are huge variations within the nation ranging from 0.8%-14.9%, depending on regions, ethnic groups and sexes [1]. The number of people living with HIV is between 1.3 million to 1.6 million. There is a big difference in HIV-prevalence between women and men: 8-8.4% versus 4.3-5.4%. Among young women, aged 15-24, the women have four times higher risk: 4.5-5.6% against 1.1-1.4% [22]. New infections for 2009 were estimated at 100,000 with 44% of the infections found among women and men living in partnerships [22]. The increase in HIV prevalence in Kenya, seen from 2003 to 2008, is probably due to lower mortality in AIDS because of increased ART coverage.

There is also a difference in HIV-prevalence between rural and urban areas: 6-6.7% versus 7.2-8.4% [22], although the absolute number of HIV-infected people is larger in rural areas since the majority of the Kenyans still live in rural areas.

A characteristic of the Kenyan HIV epidemic is the variety in HIV-prevalence related to marital status, the highest being among widows (44.4%), and the lowest for those never been married (2.4%) [22]. The HIV-prevalence is furthermore double among people living in polygamy compared to non-polygamous relationships (12.9% versus 6.1%).

Table 1. Kenya demographics, socio-economic data and HIV-data

Demographic data	Estimate	Source
Total population, 2009	37.5 million	WHO, 2010
Languages	English: official language Kiswahili: official language More than 40 indigenous languages	CIA fact book, 2010
Religion	Protestant: 45% Roman Catholic: 33% Muslim: 10% Indigenous beliefs:10%	CIA fact book, 2010
Life expectancy at birth (Years)	Men: 52 Women: 55	WHO, 2010
Literacy (%), 2000-2004	73.6	UNAIDS, 2007
% of population in urban areas	21	UN Population Division, 2008
Probability of dying under five, U5MR (per 1,000 live births)	121	WHO, 2010
Fertility rate, 2004	5.0	WHO, 2010
Infant mortality rate, IMR (per 1,000 live births), 2006	79	WHO, 2010
Maternal mortality ratio, MMR (Per 100, 000 live births	560	WHO, 2010
Socio-economic data		
GDP per capita (2006)	1 470 US dollars	World Bank
Per capita total expenditure on health (2005)	95	World Health Statistics 2008
Human Development Index (Ranking 2007/2008)	148	UNDP
Human Poverty Index (Ranking 2007/2008)	60	UNDP
Gini-Coefficient (2006)	0.57	World Bank
Transparency International Corruption index (Index and rank, 2009)	2.2; 146/180	Transparency International
HIV-data		
Number of people living with HIV	1.3 - 1.6 million	UNGASS, 2010*
Prevalence of HIV, total (% of population age 15-49; 2008-9)	KAIS* (2007): 7.4% KDHS* (2008-09): 6.3%	UNGASS, 2010
Prevalence of HIV by sex age 15-49 (2008-9)	KAIS* (2007): Men: 5.4% KAIS* (2007): Women: 8.4% KDHS* (2008-09): Men: 4.3% KDHS* (2008-09): Women: 8%	UNGASS, 2010
Prevalence of HIV among young people (age 15-24 years)	KAIS* (2007): Men: 1.4% KAIS* (2007): Women: 5.6% KDHS* (2008-09): Men: 1.1% KDHS* (2008-09): Women: 4.5%	UNGASS, 2010
HIV prevalence, adults (15-64 years) urban and rural areas	KAIS* (2007): Urban: 8.4% KAIS* (2007): Rural: 6.7% KDHS* (2008-09): Urban: 7.2% KDHS* (2008-09): Rural: 6%	UNGASS, 2010
Number of people receiving ART, both sexes (2009)	308 610	UNGASS, 2010
Number of people in need of ART, both sexes (2009)	438 000	UNGASS, 2010
% ART coverage (2009)	70.4%	UNGASS, 2010
PMTCT coverage (2009)	72.3% (58,591/81 000)	UNGASS, 2010
Percentage of most-at-risk populations that have received an HIV test in the last 12 months and who know their results	Women: 29% Men: 22.8%	UNGASS, 2010

*UNGASS=United Nations General Assembly Special Session on HIV and AIDS. Two surveys are sources for the data on HIV in Kenya: The Kenya AIDS Indicator Survey (KAIS, 2007); and the Kenya Demographic and Health Survey (KDHS, 2008-09)

In 2009, 59,000 of 81,000 HIV infected pregnant women were estimated to receive antiretrovirals (ARVs) for PMTCT, at antenatal care (ANC) making the PMTCT coverage 72% [22]. In Kenya PMTCT services are free of charge and should include HIV testing, counselling, ART preventive treatment, infant feeding support, obstetric care and family planning. There are still many challenges surrounding PMTCT in Kenya though with low utilization of ANC with only 44% of women giving birth at health facilities and loss to follow up of women who do not return for their HIV test results [22].

About 85% of Kenyan men are circumcised but there are large variations in different regions [22]. A Male Circumcision Policy strategic plan has been initiated and today 124 health centres offer free and safe circumcising services [22].

Knowledge about HIV prevention is high in Kenya. Among women and men, 75% versus 81% know that the use of condom reduces the risk of HIV transmission [22]. A number of behaviour change strategies have been implemented in Kenya and recent data show an increase in condom use, reduction in number of sexual partners and a delay in sexual debut [22]. Kenya is one of the few countries to have adopted the Rapid Result Approach (RRA). The RRA aims to, within a 90-day period, rapidly test as many people as possible for HIV. Over a three-week period in 2009, over 1.2 million people got tested and counselled [22].

The number of people receiving ART in Kenya is 308 000 out of 438 000 in need (2009). This makes the ART-coverage 70.4% [23]. There are 943 health facilities providing ART, making up 14% of all health facilities of the country. The paediatric coverage is about 24% (28 000 children).

Poverty and the Millennium Development Goals (MDGs)

The World Bank's definition of poverty is someone living with an income less than US$2 per day [24]. Extreme poverty is defined as living on less than US$ 1 per day. According to this, three billion people in the world are poor. In general, poverty and slums go hand in hand, but not always. There is an "urbanization of poverty" with a growing tendency towards poverty in the urban slum areas [13]. Most people in slums work in the informal sector, inside and outside the slums. The tendency in improving conditions for slum dwellers today is to focus on poverty in general and less on better housing and infrastructure. According to UN-Habitat, the UN section working with improvement of slums in the world, people in the slums have to be part of the decision process in how to improve the living conditions for themselves [13].

The improvement in health in the 20th century has had enormous effects in reducing mortality in the world. Huge inequalities remain, though, especially in the urban slums. The lack of access to safe water in slums makes these overcrowded urban areas extra prone to the spreading of infectious diseases [13]. For people with an impaired immune system, due to HIV or malnutrition, poor housing conditions can be devastating as TB and other diseases spread more easily in a slum [13].

In 2000 the United Nations (UN) set up eight Millennium Development Goals to be reached by 2015 [25]. Several of these goals relate to the HIV epidemic: The second MDG, to "achieve primary education", includes HIV prevention education for young people and to reduce girls' vulnerability to HIV [25]. The seventh MDG is set to "Combat HIV/AIDS, malaria, and other diseases" [25]. Within the MDGs, one of the targets is "By 2020, to have achieved a significant improvement in the lives of at least 100 million slum dwellers" [13].

The "3 by 5 initiative" was set by WHO and UNAIDS in 2003 as a goal to put three million people on ART by 2005 [26]. It was an initiative to reach global access for all patients in need for ART. Today 4.7 million people have been initiated on ART but still 58% of those in need do not get treatment [3].

Gender, transactional sex and HIV

The HIV-epidemic disproportionately affects women and children. Fifty-seven percent of all people infected of HIV in SSA are women [27]. In Kenya, women face a three times higher risk then men to be infected by HIV [1] (Table 1). Young people are most exposed to the epidemic and in Kenya, 4.5% of women aged 15-24 years, and 1.1% of men the same age group, are HIV-infected. According to UNAIDS, women are more susceptible to HIV, have less access to care and suffer more from stigma if infected [1]. Women are often the first ones to be diagnosed during ANC and hence risk being accused of having brought the virus home [27]. HIV-infected women in Kenya have a 50% lifetime prevalence of physical violence [28]. Also, women are more severely affected than men in SSA, partly because of their higher susceptibility to heterosexual transmission, but also due to age-mixing, social, legal, cultural inequities and intimate partner violence or other forms of sexual violence limiting their capacity to avoid unsafe sex practices [1].

Transactional sex, i.e. when sex is exchanged for cash and/or material goods and/or alcohol, increases power differentials in sexual relationships between women and their sexual partners, the likelihood of multiple sexual partners and unsafe sex practices [29-31]. The relatively common practice of multiple concurrent partnerships as well as transactional sex which both play a significant role for sexual transmission of HIV in many high-burden countries on Southern and Eastern Africa, must thus be differentiated from the more rare occurrence of sex work. Sex work is more important in areas with more concentrated endemics of HIV such as South-East Asia and West Africa where for example in Mali 35% of all sex workers were HIV-infected in 2006 [32]. Much has been achieved in reducing HIV transmission in vulnerable groups, such as sex workers, through the promotion of increased condom use for example in Thailand [33]. But nevertheless, only 60% of all sex workers were estimated to have been reached by prevention programmes in 2007 [32].

People living in slums are highly vulnerable to the HIV epidemic. Compared to rural residents in Kenya, people living in slums start having sexual intercourse earlier in life, have more sexual partners and have less knowledge on how to use preventive measures in contracting HIV [34]. Amuyunzu-Nyamongo et al (2007) explored the situation for women in the Nairobi informal settlements and found that the coping strategies that women living with HIV used to survive the poor living conditions were to engage in sex work and selling illicit liquor [27]. Further, the insecurity and the lack of child care in the slums hindered the women from working and getting sufficient income [27].

Traditional medicine and religion

Traditional medicine often seeks understanding of the underlying cause of disease [35]. There are two different theories often referred to in the literature: personalistic and neutralistic. Personalistic theories try to explain disease as attributable to some kind of external force (supernatural, human

or non-human). In neutralistic traditions there is more a question of imbalances of elements in the body. African traditional medicine is often explained by personalistic theories [35]. It has two branches, belief in the supernatural and herbalism [36]. In the supernatural branch, the traditional healer uses occult medicine and works as a spirit medium. Health problems as often explained by curses, witchcraft or former existence (re-incarnation). In the other branch, a herbalist uses different botanic remedies with therapeutic effects, known for many generations and not documented in any extensive way [36].

Besides traditional medicine, religious activities and beliefs are also important components for many people in countries highly affected by HIV/AIDS in SSA. In Kenya, 75-80% of the population is Protestant or Catholic, 10% are Muslims and 10% belong to various indigenous religions [37]. The use of spiritual healing is not well studied but important to many people in Kenya and significant in the STD-management in Nairobi [38].

Despite the widespread use of TM and the vast influence of religion in the lives of many people, little is known about its impact on adherence and discontinuation of ART in SSA [38, 39]. Zou et al (2009) found that among 438 church-members in Tanzania, stigma was associated with religious beliefs but religious factors were not related to the hypothetical willingness to start ARV [40]. In another study from Uganda, only 1.2% of ART users discontinued their treatment due to religious factors [39]. The importance of collaborating with faith leaders has been raised as an important aspect of retaining patients on treatment in SSA [39, 41].

Traditional medicine versus western medicine

Long before the HIV epidemic came to Africa, most people went to see a traditional doctor primarily and not the "western doctor" [42]. Today, in some African countries as much as 70% of the population receive treatment, social support and counselling from traditional healers [43, 44]. UNAIDS states that about 60% of the people in SSA initially visit a traditional health practitioner for their sexually transmitted diseases, including HIV [45].

Traditional health practitioners are often involved in several different practices such as herbalism, spiritualism and healing. Many people in SSA prefer traditional medicine due to familiarity, trust, accessibility, expense and the perceived cause [46]. In spite of being the primary supplier of health care in SSA, traditional medicine has received little attention by researchers and policy makers.

There is a shortage of human resources in many SSA countries [47]. In SSA the ratio of traditional doctors to the population is 1/500 and for biomedical doctors the ratio is 1/40000 [48]. It has been argued that one million extra people in the health care work force are needed in SSA and 4 million globally [7]. While health systems in this region lack human resources to face the increasing needs to care for people living with HIV [8, 49, 50], the World Health Organization (WHO) has since 1974 acknowledged the importance of traditional health practitioners in general, and also, in recent years, suggested that the practitioners become more involved in standard HIV-care [42, 45, 51]. The objective of WHO has been to integrate TM with national health systems, expand the knowledge base on TM and promote rational use of TM [42, 48]. Unequivocally TM is a part of the SSA health system and has to be taken into account when dealing with HIV/AIDS. UNAIDS has developed guidelines for collaboration between traditional and biomedical medicine [52]. Many believe that TM is the key to fighting the HIV-pandemic in Africa [53]. Others point to the

dangerous customs used by some practices of TM like using herbs that can even harm and kill patients instead of treating them [54]. Despite the concern from many researchers, few studies have actually been performed about the efficacy of TM on HIV [55].

Collaboration between these two practices (traditional and biomedical) has been initiated in many SSA countries but reservations on the results have been raised [56]. Kaboru et al (2006) explored the collaboration between biomedical and traditional health providers (BHPs and THPs) in Zambia and concluded that collaboration between BHPs and THPs was quite uncommon and that lack of trust from BHPs towards THPs existed. On the other hand 40% of BHPs (total of 152) were positive to extended collaboration [57]. There is a need for political commitment in fighting stigma against THPs and to distribute adequate roles for all actors, both THPs and BHPs [57].

The role of TM on discontinuation of ART in SSA has not been studied extensively but thought to influence people's lives in general in SSA [58]. Roura et al (2009) found that patient retention in an ART programme in Tanzania was influenced by factors like traditional medicine and religious beliefs in society [59].

Funding for HIV

In 2007 the global annual expenditures on HIV rose to US$ 13.7 billion as compared to US$ 300 million in 1996 [60]. Although an enormous increase in funding, primarily from international donors, the estimated need for 2010 was US$ 25.1 billion [60]. The single largest governmental donor is the US PEPFAR programme (President's Emergency Plan for AIDS Relief) [61], which is an umbrella for all the USA Government's HIV programmes. Multilateral funding organizations distribute the money they get from different national governments. The biggest multilateral organization is the Global Fund to Fight AIDS, Tuberculosis and Malaria [62]. The second largest multilateral donor is the World Bank [20]. Four per cent of the HIV funding comes from private donations like the Bill and Melinda Gates Foundation, religious groups and non-governmental organizations (NGOs). Ironically, out-of-pocket expenditure by patients and their relatives on user fees, drugs etc accounts for a much larger share of health costs in poor societies than in high-income countries, while domestic funding for health from local governments accounts for a smaller proportion [60].

AIDS has been devastating for the health systems in resource-poor settings, especially in SSA [63]. The already fragile health systems in SSA, with lack of human resources, limited supplies of medicines and bad management, have been extensively overburdened by the HIV epidemic. In many resource-limited settings, neither full blood counts or CD4 counts are available, much less viral load measures which are often prohibitively expensive unless the ART programme is sponsored by an external donor or research institution[64].

ANTIRETROVIRAL TREATMENT (ART)

Several prevention interventions against HIV transmission exist: behavioural change programmes, condom use, HIV-testing, safe blood supply and male circumcision [65]. Although prevention is an important part in responding to the HIV epidemic, only 20 % of the people in need had access to HIV prevention programmes in 2009 [65].

The first drug against HIV (Zidovudine, AZT) was introduced in 1987 [66]. In 1995 the first protease inhibitor was accepted by the American Food and Drug Administration [67] and the major step towards an efficient HIV therapy was taken in the end of 1995 when treatment changed from dual to triple therapy or so called highly active antiretroviral treatment (HAART, in this thesis called ART). The combination of different ARV drugs has reduced mortality and prolonged survival for HIV-infected individuals dramatically [68]. Since ART cannot eradicate the virus completely [69], persistent viral suppression by continuous daily intake of ARVs is essential for the drugs to be long-term efficient and to avoid resistance development [70]. The goal with ART is to suppress viral replication to immeasurable levels (now normally defined as a viral load < 50 copies/ml [71] in order to reduce or avoid further depletion of CD4+ T-cells and chronic immune activation, enabling a reconstitution of the immune system and prolonged survival [72].

Today, there are six classes of ARVs used to treat HIV: Nucleoside/nucleotide analogues (NRTI), non-nucleoside reverse-transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitors (or "entry inhibitors"), CCR5 antagonists and integrase inhibitors. Standard 1st line ART usually combines two nucleoside analogues (NRTIs) with either one PI or one NNRTI [73]. WHO recommends the combination of at least three different ARV drugs for HIV-naïve adults to reduce the risk of drug resistance:

- AZT + 3TC + EFV
- AZT + 3TC + NVP
- TDF + 3TC or FTC + EFV
- TDF + 3TC or FTC + NVP

(AZT=zidovudine (also known as ZDV), 3TC=lamivudine, EFV=efavirenz, NVP =nevirapine, TDF=tenofovir disoproxil fumarate, FTC=emtricitabine) [74])

The advantages and disadvantages of the three most common ARV classes are listed in Table 2.

Table 2. NRTI, NNRTI and PIs. Advantages and disadvantages. (Adapted from The Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009 [73])

ARV Class	Advantages	Disadvantages
NRTI	• Established backbone of combination antiretroviral therapy. Many studies performed. •Long history of use worldwide.	•Rare but serious cases of lactic acidosis with hepatic steatosis reported
NNRTI	• Saves PIs and raltegravir for future use • Long half-lives • Less expensive than PIs	• Potential for cross resistance • Transmitted resistance to NNRTIs more common than for PIs • Low genetic barrier to resistance (single mutation resistance for efavirenz, nevirapine, and delavirdine): greater risk of resistance at time of viral rebound folllowing treatment interruption • Skin rash • Potential for drug interactions
PI	• Higher genetic barrier to resistance against PIs followingviral failure (boosted PIs)	• Metabolic complications (e.g., dyslipidemia, insulin resistance, hepatotoxicity) • Gastrointestinal adverse effects • Potential for drug interactions • More expensive than NNRTIs • Sometimes needs refrigeration in hot climates

Treatment failure

Treatment failure to ART is defined as failure to suppress the viral load below immeasurable levels or viral rebound, a decline or suboptimal response in immunological parameters (CD4 count) or re-occurrence or worsening of clinical symptoms [71], or death. Although monitoring clinical parameters and CD4 counts has a lower sensitivity than viral load in terms of predicting treatment failure [75], viral load measurements are often not available in low-income settings.

Viral failure can occur as a consequence of suboptimal treatment adherence, treatment interruption or due to viral replication in spite of treatment either due to drug resistance or suboptimal drug exposure e.g. caused by drug interactions, altered drug metabolism, or decreased drug absorption [76]. Treatment interruption may be caused either by the patient who fails to take the drug as prescribed or because he or she cannot access the drugs for different reasons such as the frequent stock-outs of ARVs and essential drugs that often occur in many African health systems [77]. Exploring reasons for sub-optimal adherence and drop-out from ART in a resource-poor urban African setting is the focus of this thesis and the other risk factors that may cause sub-optimal drug exposure and affect the virological response will not be discussed in detail in this thesis but the most common reasons have been listed below:

- Pre-existing resistant virus [78]
- Acquired drug resistance [79]
- Drug stock-outs at health facility level [77]
- Drug interactions [80]
- Altered drug metabolism [81]
- Decreased drug absorption [82]
- Advanced disease stage [70]
- Low CD4-count pre-treatment [83]
- High viral load pre-treatment [83]

Side-effects

All ARV drugs are associated with one or more side-effects. Common initial side-effects are headache, nausea, diarrhoea, skin rash and vertigo [84]. Many people can handle these problems if aware they will pass. However, this assumes a well-informed patient, something that is easier to achieve in a well-functioning health system but more difficult to attain in a low-income country where patient illiteracy and lack of health staff is a reality [85]. The long-term side-effects induced by ARV drugs include fat redistribution, development of diabetes, high cholesterol and weight gain or loss [86]. Less is known about long-term effects of these metabolic changes as regards developing stroke, coronary syndromes and kidney failure, well known to be associated with metabolic syndrome in high income countries but less investigated when it comes to long-term effects of the ARV drugs [87, 88]. There are also rare, but potentially life-threatening, side-effects associated with ARVs such as allergic shock, hepatitis, pancreatitis, bone marrow depression and kidney failure [84].

Drug resistance to ARVs

Effective combination ART is crucial in order to avoid development of drug resistance that easily arises during insufficient non-suppressive ARV drug exposure. The major reason for low drug exposure is sub-optimal adherence to the prescribed treatment regimen [79].

Several inherent characteristics of HIV make this virus highly prone to genetic mutations. In untreated individuals, the rate of viral replication is very high and new cells are being infected at an enormous speed [89]. The heterogeneity of viral populations in the same individual is also high and the enzyme responsible for the crucial transcription of viral RNA genome into DNA- the reverse transcriptase - is very prone to errors [79]. As a result, point mutations occur in the HIV-genome 10 000 to 100 000 times per day [90]. Resistance causing reduced susceptibility to ART is the result of mutations in the viral proteins targeted by the ARV drug(s) [79].

Single mutations may cause both in-vitro and in-vivo drug resistance but often multiple mutations are needed to cause clinically important drug resistance resulting in treatment failure. HIV tends to develop resistance first to the agent with the lowest resistance barrier, which is often NNRTIs or NRTIs. Resistance to ART can occur to all different drug classes and limits their efficiency [91, 92]. When resistance to ARVs develops, HIV variants with resistance mutations often replicate better than a wild-type (non-mutated) virus, and therefore often become the dominant strain as long as the patient continues with the drug to which resistance has occurred. The phenomena of cross-resistance, i.e. resistance to one drug in a certain ARV class that also causes resistance to other similar types of drugs in the same ARV class, is perhaps especially problematic in poor-resource settings with limited alternative treatment regimens [79].

Resistance mutations may either be pre-existing at the time of infection or arise later due to poor adherence or other reasons. Once a resistant strain has developed, it can continue to replicate despite adequate plasma concentrations of ARVs. Primary resistance is the same as transmitted resistance, i.e. when a person is infected by a viral strain with pre-existing resistance to one or several ARVs. Most often such resistance mutations occur during sub-optimal ARV treatment, but some HIV strains are naturally resistant to some ARVs. However, acquired drug resistance that has developed in the same individual who is experiencing treatment failure is thought to be much more important than primary resistance.

There are two types of diagnostic testing for HIV drug resistance: First, genotyping that detects mutations in key genes, and second, phenotyping that measures susceptibility of the virus to ART [79]. In the genotypic test the genetic code of a patient virus is compared to the wild-type. A phenotypic resistance test is a time-consuming and costly process where increased concentration of a drug is added to a patient's HIV culture and the viral replication is compared to that of the wild-type. Genotypic testing is the recommended resistance testing for ART naïve patients or patients with suboptimal virologic response [73]. It is faster and less expensive then phenotypic testing, but the later is preferred for patients with complex drug resistance mutations patterns [73]. Large-scale drug resistance to first line ARVs would have serious public health consequences, especially in resource-poor settings with high burdens of HIV[79] where both resistance testing and alternative ARV class regimens are rarely affordable.

ART and nutrition

Before the introduction of ART the HIV wasting syndrome or so called "slim" was one of the most common AIDS manifestations accounting for up to 18 % of AIDS-defining conditions. Low body mass index is a predictor of mortality when initiating ART [93]. Studies after the introduction of ART have shown that this problem still exists in spite of the huge impact of ART in reducing mortality [94]. The weight loss associated with HIV still remains a serious clinical problem [95]. The correlation between mortality and the nutritional status of HIV-patients is well known. Weight loss is associated with lower CD4 cell counts and is an independent predictor of mortality but the mechanisms are complex and seem to have a multi-factorial aetiology [96]. Nutritional guidelines are available although there is an ongoing debate about exactly how to do nutritional assessment and how to monitor the patients.

There are a number of interactions between food and ART [97]. Some ARV drugs should be taken on an empty stomach and some with food. In one study, Damle et al (2002) showed that the bioavailability of didanosine (an NRTI), was reduced by 20-25% when eating [98]. Some ARV drugs must also be taken at exact times of day, and some with special food instructions, in order to properly have effect on the HIV virus [99, 100]. Nieuwkerk and colleagues found that only half of their ART patients followed specific schedules and food instructions and that this was associated with lower drug exposure and increased risk of viremia among treated patients in the Netherlands [99].

UPTAKE: INITIATION OF ART

Stringer et al (2006) showed in their study from Zambia that of 16 200 patients started on ART, 1 142 died (7%) during the study period of 1.5 years. Of these patients 792 (71%) died within the first 90 days of ART indicating they were (1) diagnosed with HIV too late or (2) started up on ART too late and that their AIDS progression was too advanced to survive, even on ART [101]. The uptake (initiation/opt in) of ART for those patients who need it is thus a very important part of the response to the HIV epidemic.

Barriers to ART uptake

Little is known about low uptake of ART and most research on barriers to uptake has been performed in resource-rich countries [102]. In low-income countries there are some identified barriers to ART uptake [103]:

- Cost [104]
- Food insufficiency [105]
- Distance to clinic [106]
- Women's lack of decision-making power or fear of intimate partner violence [107]
- Stigma [108]
- Fear of the medication [105, 108]
- Lack of information [108]
- Belief in traditional medicine [46]

ADHERENCE TO ART

Definition

Adherence is often defined as "the extent to which patients take medications as prescribed by their health care providers" [109]. Adherence is separated from "compliance" since compliance indicates a more passive patient while adherence implies that there is a contract of understanding between the patient and the health care provider. Rates of adherence are often reported as the percentage of prescribed doses of medicine taken over a specified time-period [109]. Low adherence is costly when it results in suboptimal clinical response or symptom relapse: in the US alone, hospital admissions due to low adherence of all medications (not just ART) cost approximately US$ 100 billion per year [109].

Relationship between viral load, drug-resistance, survival and adherence

Adherence to ART is crucial for treatment success among HIV patients [110-113]. It is the most important predictor of virologic suppression [114-117], drug resistance development [76, 118-121] and disease progression causing premature morbidity and mortality [122-124] (Figure 2). Treatment with unboosted PIs requires almost perfect adherence for virologic suppression [117] while more potent NNRTIs and boosted PI therapies have resulted in virologic suppression at lower levels of adherence [114, 125].

It appears that the relationship between adherence to ARVs and drug-resistant mutations is bell-shaped with the highest frequency of developing resistance being linked to imperfect adherence levels of 70-90% [76, 121, 126]. At the public health level, development of drug resistance has been shown to increase mortality [127] (Figure 2).

ART non-adherence creates a substantial challenge in resource-poor settings like urban slums. Development of drug resistance due to non-adherence is hard to fight with the available treatment alternatives in settings where second or third line treatment is difficult or too expensive to access.

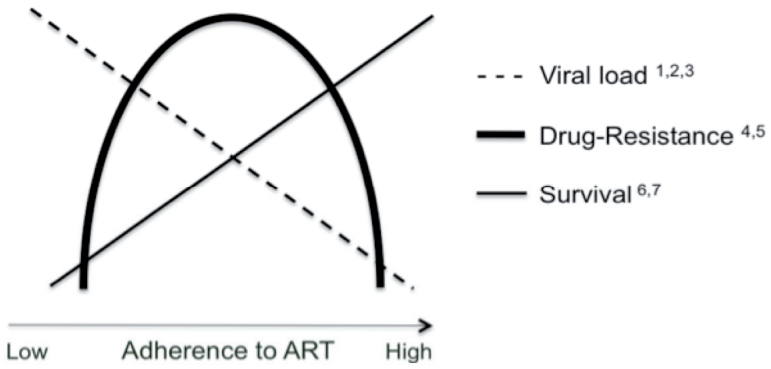

Figure 2. *Schematic figure of the relationship between adherence, resistance, viral load and survival.*
1. Arnsten et al (2001), 2. Bangsberg et al (2000), 3. Paterson et al (2000), 4. Bangsberg et al (2004), 5. Harrigan et al (2005), 6. Bangsberg et al (2001), 7. Hogg et al (2002) [110, 116, 117, 120-123]

Theories on readiness, motivation and adherence

Health belief model

The most commonly used theory that has been developed to explain and predict health behaviours is the Health Belief Model (HBM) [128]. The most important concepts of the HBM are: perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action and self-efficacy [129]. According to the model, patients will act to prevent disease, if they feel that they are susceptible to the condition (i.e. deterioration to AIDS/death if not taking ART) if the condition is believed to have serious consequences for the patient (i.e. not taking ART will make the patient sick), if the patient feels that the action they will take can reduce their susceptibility to the condition (i.e. the/she feels that adhering to ART will reduce the risk for AIDS/death) and if the patient feels that the eventual barriers to taking the action (adhere to ART) are outweighed by the benefits for the patient. Cues (events that trigger action) and self-efficacy i.e. "the conviction that one can successfully execute the behaviour required to produce the outcome" [128].

Readiness to start ART

Adherence is a very important part of treatment of HIV but before adherence becomes an issue to consider, it is important that the patient feels *ready* to start treatment, so called readiness. Readiness to treatment includes that the patient feels ready to initiate treatment, is willing to take responsibility for, and to maintain treatment.

Readiness for starting treatment has been defined as: "a conscious awareness on the part of the individuals that they, of their own will, have considered and determined that a particular change will be beneficial. In addition, the individual has identified barriers that may prevent this behaviour from occurring and has accepted responsibility for initiation of the behaviour.
Finally, a sense of control and impending action on the part of the individual must be present" [130].

This means that the patient should be aware this specific change in life, e.g. in this case taking ARVs, will mean something positive or put in another way, having reached readiness requires that "an individual's capability for change (i.e. the client has the skills to change) and faith that change both is possible and will produce a positive outcome" [131].

The theoretical underpinning that explains the readiness concept include several theories of motivation and change such as the Wellness Motivation Theory [132] and the Trans-theoretical Model of Change [133]. In several of these theories the concept of a trigger, or a cue, is an often-mentioned component [132].

There is a close relationship between motivation and readiness and a special form exists called "motivational readiness". "Motivational readiness" is described as "an individual's readiness and willingness, or behavioural readiness, to engage in the behavioural practices required to produce a desired outcome" [134]. This is said to emphasize the importance of a patient being ready and motivated to start a treatment that will continue for life in order to have a high adherence rate and a positive outcome of the treatment. Guidelines exist to help medical staff to assess whether or not a patient is ready for treatment [135]. What is well-known though is that physicians tend to overestimate the motivation and adherence rate of the patients in general [136].

Enriquez et al (2004) found that within a group of non-adherent patients all experienced a specific event, a trigger event, which made them change their non-adherence behaviour. They had all failed several times to adhere to ART treatment but something made them change their behaviour and remain adherent to ART over a long period of time [137]. This event could be, e.g. a life-threatening experience in deterioration of health [137]. A trigger event is in this thesis is defined as an event or a person that influences a person fundamentally, something the person can describe in detail even years later. In order for this to happen a process containing five components needs to occur: The patients' attitudes towards the treatment need to change, the patient should find the right health care provider, create a support system, gain control over life and form goals [137]. In this theory [137], trigger events are assumed to initiate positive health behaviour change [138].

Patient's readiness to start treatment for HIV in resource-poor settings is rarely accounted for and no particular study on the issue has been performed.

How to measure adherence

There is no consensus regarding which adherence measure to use [139] and methods include indirect measures (e.g. pill counts, self-reports, electronic monitoring devices and medication refill rates) [117, 140, 141] and direct measures (e.g. observations, drug monitoring and biological markers) [142]. Many of the above methods are costly and not well evaluated [32]. Self-reported measures, however, are quick and inexpensive [143], and have been shown to predict clinical outcome [144] and have a significant association with viral load [143]. However, self-reports and pill counts tend to over-estimate adherence [144, 145], while medication refill rates need electronic pharmacy data systems in order to be efficient and are not common in SSA [109].

Through questionnaires, diaries and interviews patients can report how many doses of their pills they have missed during a specific time interval. They can also be asked questions on different aspects of adherence. Self reported adherence has both high sensitivity and specificity [146] but tends to over-estimate adherence levels through recall bias and social desirability (patients telling the health care provider what he/she think they want to hear) [147].

Several studies have shown that not only dosing, but also the exact timing and following special instructions, are important aspects of adherence and impact on viral load [99, 100]. An adherence index is sometimes used to account for different aspects of adherence [139]. Mannheimer et al (2006) created an index, "The CASE Adherence Index", composed of three self-reported adherence questions [139]:

- 'difficulty taking HIV medications on time (no more than two hours before or two hours after the time your doctor told you to take it)'.
- 'average number of days per week at least one dose of HIV medications was missed'
- 'last time missed at least one dose of HIV medications'

The CASE Adherence Index was strongly correlated with decreasing viral load and increase in CD4 count [139].

Calculating adherence from administrative data
There are several ways of calculating adherence from administrative data like pharmacy databases. There are limitations with administrative data such as the fact that it only calculates possession, not how many pills a patient has actually taken [148]. It has furthermore not been shown to correlate with patient's self-reported adherence [149, 150]. Despite this, administrative data calculations are non-expensive, objective, convenient and non-invasive [148]. Hess et al (2006) compared different measures of calculating adherence in their review of current literature[148]. There were advantages and disadvantages with the different calculations but CMA, CMOS. MPR, MRA, CMG and PDC (see Table 3) all showed the same adherence. They recommended the Medication Refill Adherence (MRA) since it is simple, requires few data and has been shown to provide the same adherence results as other refill adherence measures [151]. When there is high attrition they recommended the Continues, Single Interval Measure of Medication Availability (CSA) [152].

Barriers and facilitators to adherence

There are several known barriers and facilitators to adherence in both high-and low-income countries as depicted in Table 4.

DROP-OUT, DISCONTINUATION AND RETENTION

Definitions

A prerequisite for adherence to ART is long-term retention in ART programmes. The opposite of retention is drop-out. Drop-out from ART in this thesis is used synonymously with attrition, defaulting or discontinuation from ART. Drop-out, discontinuation, defaulting or attrition from, can further be divided into four categories [153]:

- Death
- Loss to follow up (LTFU): Including missing scheduled appointments or drug refill
- Still in programme but stopped taking medicines
- Transfer to other clinics continuing taking ART

Table 3. Measurement of adherence from administrative data. Different measures, their formulas and values. Adapted from Hess et al (2006) [148]

Measure	Formula	Value
CMA = Continuous Measure of Medication Acquisition	cumulative days' supply of medication obtained/total days to next fill or to end of observation period	Adherence value for cumulative time period
CMG = Continuous Measure of Medication Gaps	total days of treatment gaps/total days to next fill or end of observation period	Non-adherence value for cumulative period
CMOS = Continuous Multiple Interval Measure of Oversupply	total days of treatment gaps (+) or surplus (–) /total days in observation period	Non-adherence value for cumulative period allowing for surplus
CR = Compliance Ratio	(total days supplied – last days' supply)/ (last claim date – first claim date) x 100	Adherence value for period between fills
CSA = Continuous, Single Interval Measure of Medication Availability	days' supply obtained at beginning of interval/days in interval	Adherence value for interval of study participation
DBR = Days Between Fills Adherence Rate	1 – ([(last claim date – first claim date) – total days' supply]/ (last claim date – first claim date)) x 100	Overall adherence percentage
MPR = Medication Possession Ratio	days' supply: days in period	Ratio of medication available
MPRm = Medication Possession Ratio, modified	[total days supplied/(last claim date – first claim date + last days' supply)] x 100	Adherence percentage, adjusted to include final refill period
MRA = Medication Refill Adherence	(total days' supply/total number of days evaluated) x 100	Overall adherence percentage
PDC = Proportion of Days Covered	(total days supply/total number of days evaluated) x 100%, capped at 1.0	Percentage of days with medication available
RCR = Refill Compliance Rate	[(sum of quantity dispensed over interval/ quantity to be taken per day) x 100]/number of days in interval between first and last refill	Overall adherence percentage

Many definitions of loss to follow up (LTFU) from an ART programme have been used with different thresholds ranging between 30 and 120 days [101, 153-155]. Chi et al (2010) suggested 60 days after the last visit should be used since this has the lowest level of misclassification (highest combined specificity and sensitivity) of LTFU [156]. They analyzed patients that were said to be LTFU in a Zambian cohort of 33,700 patients on ART. Patients were then followed-up and classified as either "true" LTFU, that is, not returning to program; or "false" LTFU. The best threshold in LTFU days with the lowest misclassification (highest combined specificity and sensitivity) was 56 days, but 60 days was within the same marginal.

Retention in ART programmes

Retention in the ART programme is of major importance for survival among HIV patients. Discontinuation of ART, when any signs of AIDS have been diagnosed, most often leads to a rather rapid death [157]. Braitstein et al (2006) found that patients in low-income countries have four times higher risk of dying in the first month on ART, as compared with patients in high-income countries [158]. Low CD4-count at baseline is associated with higher mortality [155] and also a predictor of low retention in ART programmes [159].

Rosen et al (2007) analyzed 33 patient cohorts from 13 African countries and found that on average only 60% of patients were retained in ART programmes after two years from treatment initiation [153]. Loss to follow up and early death were the major causes of drop-out. The authors stressed the importance of early initiation of ART and better tracing systems [153, 160]. Similar data have been presented in a review by Tassie et al (2010) with a retention in SSA ART-programmes of 75% at 12 months and 67% at 24 months [161].

Barriers and facilitators for retention in ART care

Personal motivation and self-efficacy have been shown to facilitate retention in ART programme [59], but only a few studies have focused on the issue. Harries et al (2010) summarized suggestions of strategies to improve patient retention in ART programmes in SSA [162]. Some of the recommendations were: (1) simple and standardized monitoring systems to track patients; (2) reducing early mortality; (3) uninterrupted drug supplies (4) simple, non-toxic ART regimes; (5) decentralization of ART health facilities; (6) reducing indirect costs (transportation) [162].

Barriers to retention in ART-programmes in SSA are: formal and informal costs, severe poverty, side-effects, non-disclosure, long waiting times, alcohol abuse, use of traditional medicines [105, 163, 164], denial of HIV-status and lack of knowledge about HIV-progression [59], high transportation costs [165], use of ART prior to the current regime, hospitalization, less than 1 year on ART [166], stigma and care dissatisfaction [167].

It is often more difficult to trace patients that are LTFU in resource-limited settings especially in informal urban settings with high mobility, where people also do not have any exact address (streets or numbers), often lack telephones and many of the patients die before their reason for lost to follow up (LTFU) is identified [155], but early tracing *can* improve patient outcome [168] (Table 4).

There are specific challenges to keeping patients on ART care in the informal settlements in SSA given the high mobility, poverty, lack of family support structures, mixed target populations and

higher risk behaviours including alcohol and drug use. However, very little research addressing these challenges in urban slums has been done in SSA [163, 164, 169].

Table 4. Barriers and facilitators to ART adherence and retention in ART care.

Facilitators	Barriers
Ability to fit ART into daily life schedules [163]	Absence of social support [170]
Accepting HIV status [169]	Being away from home [163]
Access to health care [171]	Belief in healing [39]
Belief in treatment [163, 164, 169]	Complex ART regimens [172]
Simple regimes [169]	Decreased quality of life [169]
Social support [173, 174]}	Denial of HIV diagnosis [163]
Understanding need for strict adherence [169]	Depression [173]
	Drugs or alcohol [175]
	Fear of disclosure [169]
	Forgetfulness [169]
	Hunger [164]
	Lack of food [108, 176]
	Long waiting times at clinic [163, 164]}
	Low access to medicine [169]
	Young age (<35)[170]
	High daily pill burden [169, 170]}
	Need to maintain social support [177]
	Side-effects [178]
	Transportation cost [164]
	Stopped taking when feeling better [108]
	Treatment related cost [177]
	Use of traditional medicine [163]
	Work and family responsibilities [169]

AIMS

OVERALL AIM

The general objective of this PhD-project was to study determinants of low uptake, low adherence and discontinuation (drop-out) of ART in an urban informal setting in Kenya (Figure 3, conceptual framework).

SPECIFIC AIMS

The specific aims of this thesis were:

- To understand determinants for low uptake of ART among patients in an ART-programme (Paper I)
- To study determinants for low adherence to ART (Papers III and V)
- To understand determinants for discontinuation of ART among patients in an ART-programme (Paper IV)
- To study determinants for discontinuation of ART (Papers III and V)

During the PhD process we added one specific aim:

- To study access to ARV treatment during civil strife (Paper II)

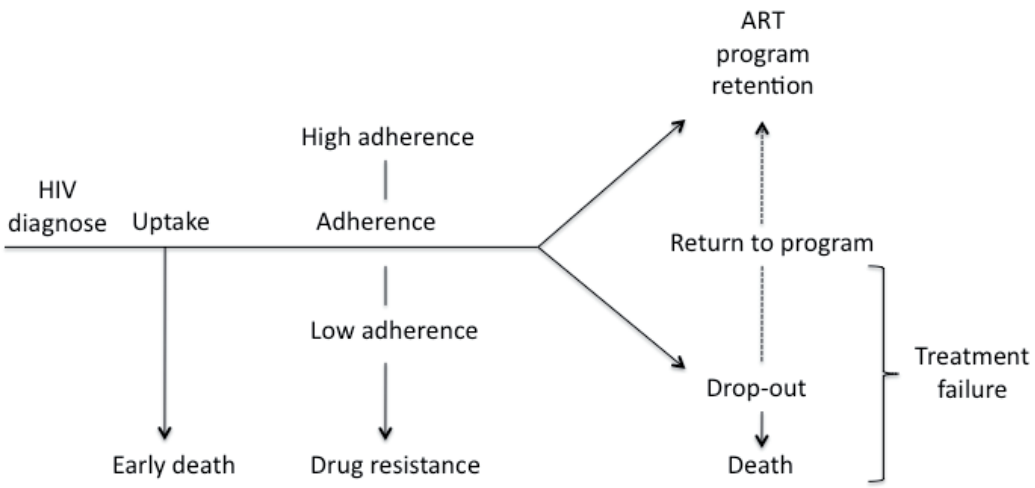

Figure 3. *Conceptual framework: Uptake of ART, adherence to ART, drop-out from ART programme and reasons for treatment failure among patients in the Kibera slum.*

CONCEPTUAL FRAMEWORK

Many patients get their HIV-diagnosis years after infection when their CD4 cell counts are low and they are already showing signs of opportunistic infections and deterioration of health. In a previous study by Stringer et al (2006) 15 000 patients starting ART in Zambia had a mean CD4 count of 143 /µl and 73% were in WHO stage III or IV [101]. Given the late diagnosis, most patients are advised to start ARV immediately (uptake), many without having enough time to accept their HIV-status and the concept of life-long treatment. Changing risk behaviour related to sexuality, food habits etcetera is also a process that normally requires a long time. Some patients start ARVs too late and die soon after initiating ARV. In the Zambian cohort, 5% of the patients died within 90 days after ARV start. As described previously in more detail, low adherence to ART is associated with the risk of treatment failure and drug resistance. Some of the patients who drop out, return to programme when having tried alternative treatment and failed or when they become too ill. This thesis focuses on: uptake of ART (Study I), adherence to ART (Study III, V) and drop-out from ART (Study III, IV, V) (Figure 3).

METHODS

THE STUDY SETTING: KIBERA, NAIROBI, KENYA

Slums

Almost one billion people, or 32% of the world's urban population, lived in slums in 2001 and the figure is predicted to double to two billion in the next 30 years [13]. In SSA urban slum dwellers accounted for 72% of the urban population in 2001 [13]. Most people who live in slums are poor, living under US$ 2 per day (the World Bank definition of poverty). People in the slums suffer from a higher degree of water-borne diseases and HIV/AIDS [13].

The United Nation's definition of slum is a: "run-down area of a city characterized by substandard housing and squalor and lacking in tenure security" [13]. The word "slum" often refers to an inner city area, which, over time, has grown and become overpopulated with mostly low-income groups. The term "informal settlement", which is often used synonymously, refers to an illegal or unsanctioned subdivision of land [13]. In this thesis "slum" is being used since the term is colloquially accepted by both people living in Kibera as well as people outside, referring to the area. It is by no means meant to stigmatize the people living there. Slums are characterized by social and economic isolation, overcrowding, irregular land ownership, bad housing, insufficient access to safe water, low sanitary standards and inadequate health care [179]. Further, slum inhabitants have always been associated with high crime rates but today policy makers and researchers see slum dwellers more as victims of organized crime then being the perpetrators [13]. Despite all this, living conditions have improved in some slum areas in Africa in recent years and in for example the Khayelitsha slum outside Cape Town, South Africa, some parts of the slum have electricity and running water and fairly adequate housing.

Because of their informal status, the urban slums in Kenya are underserved in terms of health care, sanitation, water and security [180, 181]. There are many different health care providers but there is no coordination between their different activities, often resulting in duplication of services and a competition for HIV patients in turn leading to a waste of resources and difficulties in terms of planning for health care services. Religious institutions and many non-governmental agencies are involved in the provision of different types of 'vertical' health services to the Kibera citizens. Despite this, or because of the many actors, the under-five mortality for children in the Nairobi slums is four times higher than for the rest of the population [182]. This is serious given that Kenya's overall child mortality indicators are higher than those of surrounding countries with lower GDP/capita.

General description of Kibera

The name Kibera comes from the Nubian word for forest, Kibra. Kibera (Figure 4) is one of the oldest slums in Africa situated in Nairobi, Kenya, and is supposed to be the biggest slum in Africa but exact population data is hard to find due to its informal status. The figure of one million is often mentioned by UN and NGOs, but recent data released by the Kenya Housing and Population Census from 2009, says this figure is grossly exaggerated and that the population is more likely to be between 220 000-250 000 [183].

Originally Kibera was a piece of land given to the Nubian soldiers by the British after the First World War. No document exists for this transaction thus leading to many disputes throughout the years concerning land ownership. Since the time when Kibera was mainly inhabited by Nubians a large migration from rural to urban areas has taken place in Kenya. Many people have settled down in Kibera and built temporary houses and gradually acquired rights to the land [184].

The housing stock in Kibera is almost exclusively made of mud and water with corrugated tin roofs. Most dwellings do not have electricity or running water. The main source of energy is charcoal and water is collected from wells around the slum. Eighty-six percent of families live in single rooms with an average family size of four [185]. Garbage piles up in the narrow lanes and sewage canals are lacking. The Kisumu railway line passes through the slum [186]. Poverty and unemployment are widespread and most people work in the informal sector (petty trade) [187]. Pipe borne water is very limited and seriously contaminated [188]. There are many high-risk areas of rowdy bars and large networks of sex workers. Substance and alcohol abuse is common.

Figure 4. *Satellite view of the Kibera slum in Nairobi. The area of Kibera is approximately the same size as Central Park in New York City.*

The MSF clinic

Médecins Sans Frontières (MSF) started its first HIV/AIDS activities in Nairobi in 1997, and began providing ART in May 2003 at two main locations, one inside the Kibera slum and one at the Mbagathi hospital, right outside Kibera. The community-based programme in the Kibera slum is integrated with the health services provided by the Ministry of Health (MoH) at three

health-care centres; Lindi, Kibera south health centre and Gatwekera. Patients have free access to voluntary counselling and testing (VCT). If tested positive for HIV, patients are enrolled in the MSF programme to eventually be put on ART. There are a number of support groups holding regular meetings for the patients, both organized by MSF and other NGOs.

People attend the clinics in Kibera for free VCT or diagnostic counselling and testing (DCT). A person who is tested positive for HIV is sent to a medical team for enrolment in the programme the same day. Staging is done according to WHO I-IV [189] and testing for CD4 is done. ARV information booklets are also handed out, together with 7 other information pamphlets. These are booklets on; "Keep infections away from you and your child", PMTCT, Nutrition and HIV/AIDS, "Talking about condoms", VCT, ART and "Managing the side effects". All patients receive a scheduled appointment about one week later. At the second visit to the clinic the CD4 result is made available to the patient. If the CD4 count is under 350 cells/µl the patient is confirmed eligible for ARV by a clinician and CD4 results are explained. The clinician also asks if the patient has read and understood the information booklet, if not, they review the information once more together. Also, (at the time of Study I) the patient needs to have disclosed their HIV status. If there are any medical problems at this time, the patients are treated for these and then booked for a later appointment. If no medical problems exist (opportunistic infections or other major disease), the patient is sent for the first ARV assessment, which is carried out, by a counsellor and a social worker. This meeting can involve group counselling, support group enrolment, individual counselling and a social worker visit. The social worker also tells the patient that he/she can be contacted at home if needed. The third visit at the clinic takes place about one week later when the second assessment is done, this time with a treatment buddy and/or sexual partner. A home visit by a social worker is done the same day or scheduled for later. When all requirements are complete, a schedule for ART is started. ARV starts with a two-week supply of ARV.

At the time for Study I, the first-line ART regimen was a fixed dose combination of Stavudine (d4T), Lamivudine (3TC) and Nevirapine (NVP), (Triomune®). HIV-infected individuals are provided information on ART, its side effects and are educated on the implications of therapy and the need for life-long adherence. A patient information booklet is used to facilitate this process. Blood is collected for a baseline CD4 count and the patient is requested to return in one week at which time, if eligibility criteria are met, the patient along with a guardian participates in a group counselling session (with peers) about ART, which is followed by an individual counselling session, conducted one week later. One tablet of Triomune® in the morning plus one tablet of a combination of d4T/3TC (Coviro LS®) at night is then prescribed for a period of 14 days. This is followed by one tablet of the fixed dose combination (Triomune®) twice daily. The follow up schedule is then monthly for three months, bimonthly until 6 months and by trimester thereafter. ART and laboratory tests are offered free-of-charge by MSF. By January 2006, the MSF clinics in the Kibera slum had initiated 487 patients on ART.

The AMREF clinic

The AMREF clinic was the first to provide ART in Kibera, and AMREF has offered free treatment and care for HIV-infected individuals in Kibera since the beginning of 2003. The health clinic offers preventive, diagnostic and basic health care, including services focusing on immunization, nutrition and reproductive health. An ART programme was started in February 2003 and since then the clinic has provided free VCT, PMTCT and HIV/AIDS treatment, care and support,

including nutritional support and home-based care to the Kibera population. Adherence and retention in the ART programme is supported by counsellors, post-test clubs, treatment literacy training for children and adults, social assessments and change of pill-regimes to fixed doses. Tracing of defaulted patients is done by community health workers with support from the post-test clubs. Patient eligibility for ART was initially based on WHO clinical staging only but CD4 and viral load testing were later introduced. In 2006 routine use of viral load was discontinued. The clinic faces problems with an increasing workload, staff shortages, increased complexity of ART and reduced work space leading to lower quality of services, and problem with data management and record keeping.

One medical officer, 3 clinical officers, 14 nurses, 2 nutritionists, 2 pharmacists and 8 community health care workers run the clinic. A treatment buddy (i.e. a friend or family member, known to the clinic, helping the patient taking ART) is not obligatory but patients are advised to have one. A nutrition programme provides fortified flour to HIV-infected adults and patients with TB if they have a body mass index below 18.4, and to all HIV-infected children.

Patients who present with WHO clinical stage 3 or 4, or, with a CD4-count of <250 cells/µl are eligible for ART at the AMREF clinic, according to Ministry of Health guidelines [190]. Patients' CD4 cells, clinical status and, when there are signs of treatment failure, viral load are routinely monitored by the AMREF staff. Under normal conditions, patients collect their ART from the pharmacy every 30 days. First-line ART-regimes at the AMREF clinic include stavudine, lamivudine, and nevirapine/efavirenz. Second-line regimes include zidovudine, abacavir, didanosine, ritonavire-boosted lopinavir and tenofovir (Table 5). By March 2010, the AMREF clinic in the Kibera slum had initiated 1 792 patients on ART.

Table 5. Antiretroviral medicines used at the AMREF clinic (n=1770, 2010). (Study V.)

ARV	At initiation	(%)	At last follow up	(%)
Stavudine (NRTI)	1030	(58.2)	649	(36.7)
Lamivudine (NRTI)	1596	(94.3)	1530	(97.6)
Nevirapine (NNRTI)	1590	(98.7)	1517	(85.7)
Zidovudine (NRTI)	558	(33.0)	619	(35.0)
Didanosine (NRTI)	14	(0.8)	17	(1.0)
Lopinavir (PI)	13	(0.8)	42	(2.7)

OVERVIEW OF STUDY DESIGN

In this thesis both qualitative and quantitative methods were used (Figure 5, Table 6). The main research questions were identified by our collaborating partners at the AMREF clinic who had noticed problems with low adherence and high drop-out rates. In order to better understand the extent of these issues and to gain more information about the context we initially used qualitative methods in the assessment phase trying to understand the context, population and to formulate the exact research questions. Key informant interviews were performed at the clinic with head of clinic, clinical officers, social workers, nutritionists and pharmacists. Focus group discussions were conducted with both staff and PLHIV, also part of the formative research and situation analysis.

In Studies I and IV, qualitative methods were used to explore the issues of uptake (Study I) and traditional medicine and religion (Study IV). For Studies III and V, quantitative methods were chosen after several explorative assessments had been made and the research questions had been narrowed down to adherence to ART (Study III, V) and discontinuation from ART programme (Study III, V).

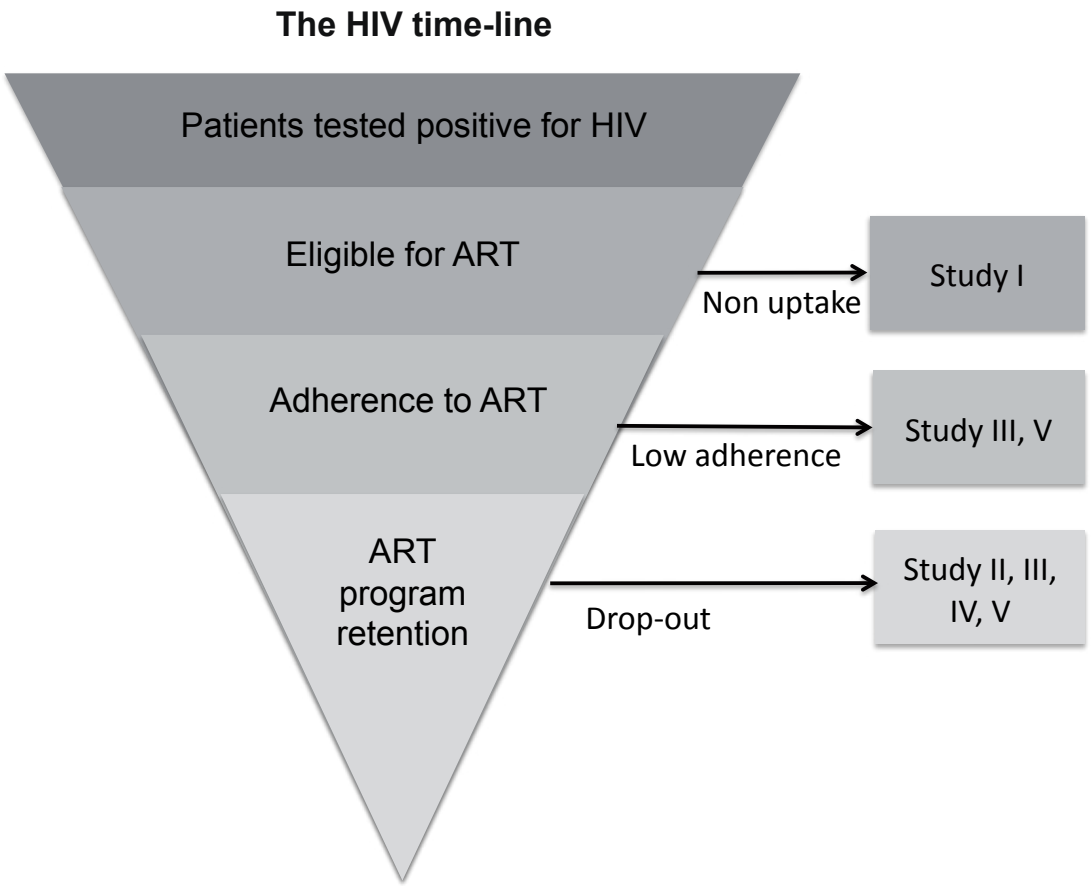

Figure 5. *Schematic figure of Studies I-V.*

Table 6. Overview of study designs used in this thesis.

Study	I	II	III	IV Explorative	IV TM and Religion	V
Design	Qualitative study	Quantitative cross-sectional survey	Retrospective cohort study	Qualitative study	Qualitative study	Prospective cohort study
Specific aim	Explore reasons for low uptake of ART	Study access to ARV treatment during civil strife	Study determinants for discontinuation of and low adherence to ART	Explore reasons for discontinuation of ART	Explore reasons for discontinuation of ART in a sub-group of patients	Study determinants for discontinuation of and low adherence to ART
Study population/ Participants	Purposeful selection of 26 patients with low CD4, eligible for ART but not returning for treatment	25 health care providers + patient records of 447 appointments	830 patients at the AMREF clinic receiving ART	Purposeful selection of 10 patients on ART and 25 staff	Purposeful selection of 20 patients, one traditional healer and one herbalist	800 patients initiated on ART at the AMREF clinic
Data collection	Semi-structured interviews	Self-administered questionnaire	Review of patient charts	Semi-structured interviews, key informant interviews and FGD	Semi-structured interviews	Interviewer mediated questionnaire
Mode of analysis	Content analysis	Drop-out rate Prescription refill calculation Multivariate analysis Kaplan Meier survival analysis	Missed appointment rate	Content analysis	Content analysis	Drop-out rate Dosage adherence Adherence index Multivariate analysis Cox regression survival analysis

DATA COLLECTION

Qualitative studies (Papers I, IV)

Data for Papers I and IV were collected by the author together with a research assistant from Kenya who speaks English, Swahili and Kikuyu and is familiar with the context of Kibera. Most interviews were conducted in Swahili, and, when needed, clarifications made in English or Kikuyu. Two of the interviews in Study V were conducted together with a social worker in another local language (Kamba). All interviews were digitally recorded, transcribed verbatim and translated from Swahili to English by the research assistant soon after the interviews. The transcribed interviews were reviewed after each interview session. The interviews were then discussed with the research assistant and clarifications were made when necessary.

Paper I

In Paper I, semi-structured, audio-recorded, face-to-face interviews were carried out (February-March 2006) with a total of 26 people, 9 men and 17 women, aged between 23 and 55 years. Three pilot interviews were performed in order to test the question guide, the technique of the interviewer and the translation/transcription process so that improvements and modifications could be made. The interviews took place either in the participant's homes (n=24) or at a nearby, neutral, location chosen by the participants (n=2). After the interview, participants were offered a lunch (Something they were not informed about when accepting the interview).

Question guides were developed for Paper I and IV to cover previously identified areas of interest with relation to; ART-uptake (Paper I) and drop-out (Paper IV). The question guides and the consent forms, both translated to Swahili, were reviewed by people from support groups, social workers, pharmacists, interns, clinical officers and the head of clinic (Appendix 1,2).

Formative research for Study IV

Prior to Study IV an explorative study was conducted in September-October 2008 in which factors influencing discontinuation from ART were explored using semi-structured interviews with PLHIV (10 patients) who had discontinued the AMREF ART-programme. The findings from these interviews were then discussed in focus group discussions with health care staff at the Kibera clinic (25 staff members in total). The findings were then discussed in a one-day seminar with about 20 staff from the AMREF clinic, researchers from Sweden and clinicians and researchers from the AMREF head office. After this session, we decided to focus on two factors influencing retention in care that were prominent in the explorative study. The two factors were: traditional medicine and religious issues. We decided to continue focusing on these main topics, conducting more interviews.

Paper IV

Following the explorative study with patients and staff, 20 semi-structured interviews were conducted (March-April 2009) with 3 men and 17 women between 27-52 years of age that had discontinued the AMREF ART-programme due to issues related to religious reasons and/ or traditional medicine. Patients were identified by community health workers (CHW) affiliated with the AMREF clinic and invited to participate in the interviews after reassuring them that denying participation would not affect their possibilities to obtain care in the future. Informed verbal consent was obtained. The CHW knew about the main reasons for these patients stopping ART and were the ones that could identify our study objects. Thus the individuals eligible for

inclusion in this study were above 18 years of age, had been on ART for at least 4 weeks before discontinuing the ART-programme and were thought to have discontinued ART mainly due to religious beliefs and/or TM. Discontinuation was defined as not showing up for treatment for 90 days or more. The average time without ART among the interviewees was 13 months.

Questionnaire survey (Paper II)

In Study II access to ARV treatment and staff experiences at the AMREF clinic in Kibera during the post-election period between 1 January and 1 February 2008 were assessed. The number of missed appointments was compared with corresponding figures for the previous year (January 2007) using patient records. A self-administered questionnaire was used to explore experiences of AMREF staff at the Kibera clinic regarding access to the clinic, safety, and alternative sources of ARV drug supply during the post-election period (Appendix 3).

Retrospective cohort (Paper III)

Paper III was a retrospective study. Data was collected from patient records at the AMREF clinic in Kibera. All patients starting ART who had completed at least their first follow up visit during the observation time from January 2005 to September 2007 were included in the study. Study patients were followed up on a monthly basis until the end-points were reached (drop-out or end of observation period). Clinical status at baseline was assessed by the Karnofsky performance scale (Appendix 4) [191]. Data on side-effects, regimen switches and opportunistic infections that would be routinely collected by the clinical officers were not used in the analysis due to a high frequency of missing data.

Prospective cohort (Paper V)

Study V was a prospective open cohort study at the AMREF clinic. All consecutive patients, HIV-infected, ≥18 years of age, visiting the clinic during the study period (9 September 2007 - 20 March 2010) and either on ART or in the process of starting ART were eligible for the study. Local clinical officers and a research assistant at the clinic were trained by the author before study initiation. The clinical officers, in collaboration with the attendant in charge, identified patients eligible for the study. One research assistant performed all baseline interviews with those patients who gave their informed consent to participate after double-checking their eligibility.

The baseline and follow-up questionnaires were developed in close collaboration with the AMREF staff, piloted on two occasions and adjusted several times after feedback from staff at the clinic with different professional backgrounds. They were based on a modified Adult Aids Clinical Trials Group adherence questionnaire, (AACTG questionnaire) [192].

The baseline questionnaire consisted of 68 closed questions covering the following socio-demographic factors: age, gender, ethnicity, religion, civil status, number of children, level of education, income, work status, living arrangements and alcohol/drug consumption (Appendix 5). The patients were asked about disclosure of HIV status and social support. One question about adherence to ART was asked: “When was the last time you missed taking any of your medications? Within the past week/ 1-2 weeks ago/ 2-4 weeks ago/ 1-3 months ago/ more than 3 months ago/ never skip medication.” Finally, they were asked questions about their reasons

for not taking ART during the last month and perceived side-effects. The same research assistant entered baseline interview dates, out-patient number and the scheduled date for a follow-up interview 6 months later, in both a logbook and the patient's medical file.

All patients, irrespective of treatment duration, were supposed to have a shorter follow-up interview once every 6 months after the baseline questionnaire. Since this was an open cohort including patients who had recently started as well as those who had longer experience of ART, we deemed that a follow-up time of 6 months would allow for every patient to have passed the initial challenging treatment period, and for those still in the programme to have gained some routine and experience of the treatment.

Adherence assessments (Papers III, V)

Paper III - CSA

In Paper III, adherence was calculated via the Continuous Single-Interval Measure of Medication Availability (CSA), that is, the daily dosage of drugs divided by the number of days in the interval from the dispensing date up to, but not including, the next dispensing date [152] (Figure 6). We retrospectively collected the *daily dosage* from existing routine patient records. The *days' in interval* were also obtained from the patient files, using follow up dates for each patient. If a patient had not returned for a drug refill for more than 90 days after the last prescribed dose, then this particular CSA-occasion was excluded, and the patient was classified as a drop-out. If a patient re-entered the programme, they could resume contributing to adherence estimates according to the CSA-formula. From the CSA-formula an adherence estimate (a proportion) for each patient and each drug dispensing occasion is derived, taking into account the differences in the number of prescribed doses. This is the recommended refill adherence measurement if a population with high attrition is studied [148]. The mean of all adherence estimates provided the overall adherence for each patient [148, 193].

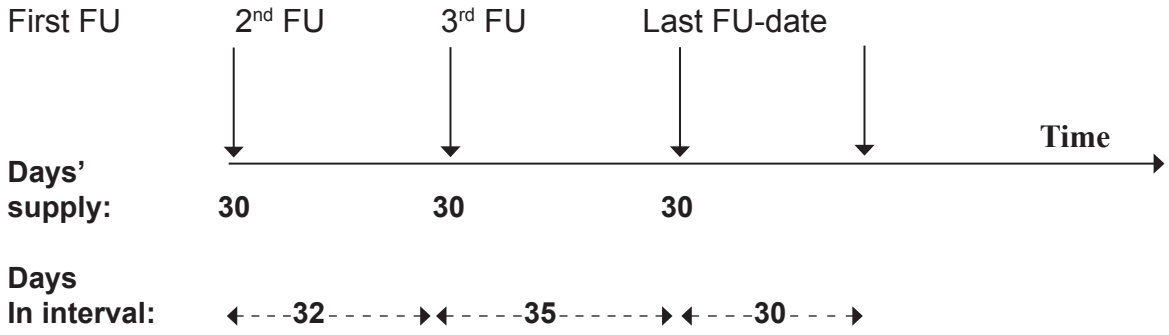

Figure 6. Study III: Example of Continuous Single-Interval Measure of Medication Availability (CSA). The first days' supply available is 30 and the days' in interval 32 giving CSA= 30/32=0.94, the second CSA=0.86, the third CSA=1.0. The mean CSA then= (0.94+0.86+1.0)/3 = 0.93 (93% adherence).

Paper V- adherence index

In Paper V, two separate measures for adherence outcomes were used: dose adherence and an adherence index. Dose adherence was based on data from the follow-up interview on number of doses per drug per day. The number of daily doses was multiplied by four to get the prescribed number of doses over the past four days and then divided by the self-reported number of missed doses on each of the past four days in order to obtain the proportion of prescribed dose actually taken over the past 4 days. At least 95% of a prescribed dose over the last four days was required to be classified as adherent.

The adherence index was based on questions from the follow-up questionnaire covering dosing, timing and special instructions. An adherence level of 95% was decided for each item: i.e. at least 4/5 for timing, 5/5 for dosing and at least 4/5 for special instructions was required to be classified as adherent. Five out of five was required for timing since the next step (4/5) meant that patients had missed all doses on one out of five days, i.e. 20% missed dose equal to only 80% adherence. Patients were defined as adherent if they scored ≥ 13/15 points on the adherence index.

The follow-up questionnaire focused on self-reported adherence to ART (as measured by a modified AACTG questionnaire [192]) (Appendix 6). First, the patients were asked the names and doses of each ARV they were taking. Drug samples were used to help patients identify their drugs since most patients did not know them by name. Then, patients were asked exactly how many pills they had failed to take over the last four days. Further, patients were asked five adherence questions: "During the past 4 days, on how many days have you missed taking all your doses?", "Most anti-HIV medications need to be taken on a schedule. How closely have you followed your specific schedule over the last four days?", "Do your ARVs have special instructions?" followed by "If yes, how often have you followed those special instructions over the last four days?", "When was the last time you missed taking any of your medications?" and "Did you miss any of your anti-HIV medications last weekend?" They were finally asked questions about their reasons for not taking ART during the last month and perceived side-effects. The AACTG questionnaire measures adherence during the last four days and during the past weekend [192].

Drop-out assessments (Papers III, V)

In Papers III and V, drop-out was defined as a patient who had not returned 90 days after the last prescribed dose. The follow-up date and number of prescribed doses were retrospectively collected from existing individual patient records. We retrieved each follow-up date, added the number of prescribed daily doses to the last follow-up date, and then added 90 days (Figure 6). This approach adjusts for differences in the prescribed number of doses.

DATA ANALYSIS

Qualitative analyses (Papers I, IV)

All the data in Studies I and IV were analyzed using latent content analysis [194, 195]. Content analysis can be manifest or latent [195]. Manifest content analysis deals with the obvious, visible components of a text, while latent content analysis refers to the underlying meaning of the text [195]. In latent content analysis the researcher works inductively, trying to explore information given in the interview and involves an interpretation of the underlying meaning of a text [195].

The *inductive* content analysis is used when there are no previous studies dealing with the research question[196]. In this process, meaning units are identified and words or phrases are grouped together in the coding, followed by condensation of meaning and abstraction, describing an interpretation on a higher logical level [195]. Data is normally generated until saturation of information is reached in the interview.

The transcribed interviews in Studies I and IV were first read several times to get a general idea of the material and to discuss the essential characteristics of the text. Coding and categorization was then performed in several stages by the author together with the other co-authors to get better inter-rater reliability. Initially key words and selected sentences were identified in the text and labeled with codes in the margins. The codes were further compared and grouped together into sub-categories. Finally the sub-categories were compared, regrouped and merged together into more analytical categories [194].

Statistical analyses (Papers III, V)

Data is routinely collected at the AMREF clinic by the clinical officer assessing the patient, and entered into a Microsoft Data Entry programme by a data clerk. This data could be retrieved to calculate drop-out (Paper III, V) and adherence (Paper III). For Paper V, data was entered by the research assistant soon after performing the interviews, using the Microsoft Office Access data entry program. SPSS for Windows, (version 15.0 - Paper III, version 18.0, SPSS, Inc., Chicago, IL - Paper V) was used for statistical analysis. Data on socio-demographic characteristics were collected for the quantitative analyses (Paper III, V). Data was double checked for validity by the author on several occasions during the study periods. Time on ART in days was calculated for all patients (Paper III, V). Mean and standard deviations were computed for numerical variables and proportions for categorical variables. Following the descriptive analysis, bivariate and multivariate logistic regression models were applied to assess the association between patient determinants and the outcome variables: (1) Non-adherence, defined as <95% as measured by the CSA (Paper III) or dose adherence (Paper V), (2) non-adherence, defined as ≤13/15 points to the adherence index (Paper V) and (3) drop-out from the programme, defined as dropping out more than 90 days after the last given dose of ART (Paper III, V).

Paper V

The association between the two adherence outcomes and baseline data on sex, age, ethnic group, religion, education (primary or secondary school), stable income (employed versus unemployed/ casual labour), living below the poverty limit (less than 5,000 Kenyan Shillings/ month, about 2 US$/day), number of people in the house, number of biological children, number of other dependants, being a Kibera resident, length of residence in Kibera, disclosed HIV status, having support taking medicines, time to clinic and having been hospitalized since starting ART was assessed in bivariate analysis. Variables with a $p<0.20$ were included in the multivariate logistic regression model and removed using a backwards, stepwise method (Wald's test). A value of $p< 0.05$ was considered statistically significant in the final models. The final goodness of fit of the model was tested using Hosmer-Lemeshow. Odds ratios (ORs) were always adjusted for age and sex regardless of p-value.

Survival analyses

A Kaplan-Meier survival analysis was performed to calculate the probability of dropping out at 6, 12 and 24 months (Paper III). The survival analysis for Paper V included a graphic presentation using a survival curve (time in days on the X axis and survival cumulative function in Y axis) with ART initiation as time zero and the event "not returning for more than 90 days after last given dose" as the loss to clinic appointment date.

A survival analysis (Cox regression model with proportional hazard assumption tested with Shoenfeld residuals) was also performed using the retrospective dataset, to calculate the hazard ratios for the drop-out, their p-value and 95% confidence intervals (CI). In a letter to the editor, another research group, Chung et al (2010), questioned our findings in the retrospective Study III where we found that Kibera residents were more at risk for programme drop-out. Chung et al had not experienced the same low retention in their ART clinic situated outside the Kibera slum [197]. In their letter to the editor they used a Cox regression model. In order to fully compare our findings from the two clinics we also performed a Cox regression analysis included in our commentary to Chung et al in JAIDS [198] (Appendix 7).

ETHICAL CONSIDERATIONS

Ethical approval for Study I was obtained from the MSF ethical review board after personal presentation in Brussels by the author following feedback from MSF and adjustments to the research protocol. For Studies II-V ethical approval was obtained from the Kenyan Medical Research Institute and this was repeated on three consecutive occasions. For all studies the Karolinska Institute's ethical review board gave their consent.

The basic principle when performing research involving humans is the respect for the individual. The person who is asked to participate in a study must be well informed, feel free to stop at any time and must have given their informed consent, verbal or written, depending on the setting. For all studies included in this thesis the participants gave their informed consent after thorough information given by the research assistant/ researcher in charge. All study participants were well informed that their anonymity would be respected throughout and after the study period. It was stressed that participation was voluntary. They were further informed that they could withdraw at any time with no effect on them, their family or on the care and treatment given.

The patients to be interviewed in Studies I and IV were approached by one of the CHWs who knew the Kibera context very well. The patients in Study I had already agreed to a home visit by a CHW when being enrolled at the MSF clinic (after testing positive for HIV). They had stayed at home and not returned for ART (which was the reason for performing Study I). They were then approached in their homes by the CHW who knew the patient well and who fully respected the decision made by the patient to participate or not in the interview (26 out of 75 patients accepted in the end to be interviewed). The CHWs were very well informed about respecting the integrity of the patients and not revealing the patient's HIV status to any neighbours. For Study IV, the patients were approached at the AMREF clinic by the CHW who, also, knew the patients well. For the assisted questionnaire interviews in Study V, the patients were asked to participate by either the clinical officer or one of the social workers who then contacted the research assistant who personally arrived to bring the patient for interview.

All questionnaires and consent forms were coded and anonymously handled. All documents were safely stored in a locker only available to the research assistant and the author.

MAIN FINDINGS

The findings from Studies I-V will be presented according to the specific aims for this thesis:

- To understand determinants for low uptake of ART among patients in an ART-programme (Paper I)
- To study determinants for low adherence to ART (Papers III and V)
- To understand determinants for discontinuation of ART among patients in an ART-programme (Paper IV)
- To study determinants for discontinuation of ART (Paper III and V)
- To study access to ARV treatment during civil strife (Paper II)

UPTAKE OF ART

Reasons for low uptake of ART (Paper I)

The categories emerging from the qualitative interviews in Study I with patients, eligible for ART, who had been offered medicine free of charge, but did not return for treatment, were:

- Fear of taking medication on an empty stomach due to lack of food
- Fear that side-effects associated with ART would make one more ill
- Fear of disclosure and its possible negative repercussions
- Concern for continuity of treatment and care
- Conflicting information from religious leaders and community, and seeking alternative care (e.g. traditional medicine)
- Illiteracy rendering patients unable to understand the information given by health workers

Fear of taking medication on an empty stomach due to lack of food

The combination of poverty, lack of food and fear of side effects from medicines was the main obstacle for most patients to start taking ART. Many patients reported having no job, which hindered them from getting money and thus food for themselves and the family. This 33-year-old woman e.g. told us about her lack of means to handle a treatment:

> I am not saying that I cannot use the treatment. In fact I do want to live longer, but sometimes I do not have a job. Other times I stay for two days without any food. That makes me afraid of using the medication.

The patients are informed by the health staff about the importance of good nutrition and to take the drugs with food. Stories about the importance of eating well when taking ART also flourished as general ideas in the community "…these drugs are very strong and you need to eat well". When already in a poor nutritional state with seldom enough food to feed the family, many people were afraid they would not have food for themselves in order to manage the ART. They expressed a feeling of not being able to take the medicines on an empty stomach: "If you start and don't get enough food you will become weak and even die" (38-year-old female).

Fear that side effects associated with ART would make one more ill
The interviewees reported fear of the side effects that would make the patients too sick to support themselves and their families, as described by this man 55 year old man:

> I have not used ART yet. A CD4 count test was done on me and they told me that it was 156 and that I needed to start taking ART. I however got scared of using them when I had heard my colleagues at the support group saying that once one started using the ART, one would get a rash, have diarrhoea and have severe headaches or even vomit. Therefore I thought it would be difficult for me to start using the ART.

Some respondents had initially been positive to ART, but had been deterred by hearing people in the community talk about side effects, such as this 26-year-old woman:

> Later I read and heard about how they affect people and decided not to use them. I decided not to start because I might get too sick and I have no one to help me.

Side-effects were seen as one of the major obstacles for patients considering ART. Many who already live on the edge of survival, in bad health, lacking money and food and with heavy responsibilities for their families, were afraid that additional adverse symptoms associated with ART would be too much to cope with. Ideas that ART could "make you infertile, impotent and weak and even kill you" were also prevalent. Many of the respondents, who refused ART, also had a spouse who had experienced side effects of ART in one way or another.

Fear of disclosure and its possible negative repercussions
According to the interviewees, stigma around HIV/AIDS in Kibera area is strong. Most felt that they had to hide their HIV status to family, friends and especially neighbours, exemplified by this 22-year-old female:

> They will just be telling other people that I am infected. If I hang up my washing, no one will want to hang theirs close to mine. They will even tell their children not to play with my children. They will abuse my children. I have seen it happen to other people. The people who are HIV positive are not accepted in the society.

Some of the patients had not disclosed their status to anybody, and the majority had only disclosed to one or two family members. Many respondents felt alone in their disease, lacked social support and had nobody with whom they could share their suffering. Fear of domestic violence as a consequence of disclosing one's status was brought up as a barrier to disclosure for women, as expressed by one 34-year-old woman afraid of being beaten by her husband:

> I would not tell him. He might get so shocked he might even harm me. He may also turn against me and tell me that I am the one who brought the disease to him

MSF required at the time of study that patients disclose their HIV status to at least one person, a so-called treatment buddy, in order to be eligible for ART. Several interviewees expressed their wish to disclose, but could not live openly with their disease out of fear of hurting the family, being rejected by their spouse or even thrown out from the family or community. They also felt that awareness about HIV in society must increase for them to be accepted and called for more community campaigns about HIV to end stigma and to raise public awareness. A 32-year-old well-educated man said: "…they have to put more effort in training people, in awareness, in public awareness about HIV and AIDS."

Concern for continuity of treatment and care
Several respondents expressed a feeling of not being ready to take ART and some did not feel motivated since they did not yet feel sick enough. At the clinic, the patients are informed to take their medication every day, not miss a single dose and that they must be prepared to take ART for the rest of their lives. This deterred some from starting ART. A 37-year-old man said: "The fact that I must use these medications on a daily basis is also something I am not sure I can follow." Others were worried that they would not be able to continue the treatment if they left Kibera and were therefore hesitant to start, as expressed by this 50-year-old man "If we decide to go to the countryside, we do not have anything there." Several interviewees also mentioned their concern about the future when MSF and other ART-providers might leave.

Conflicting information from religious leaders and community, and seeking alternative care (e.g. traditional medicine)
Instead of taking medicines many patients brought up alternative ways of seeking care and hope, mainly from religion and traditional medicine. Many respondents expressed the importance of religion; "One should believe in God. If one does not believe in God, even if one takes medication, it will not be of any use. One has to use both God and the medication." (34-year old woman), while others' had experienced or heard stories like this 30-year old woman's:

> …there is a woman who had already started using ART, then she started going to these preachers. When she started going to these preachers, she completely stopped using ART. She believed that she was not sick and wanted the preacher to cast out the evil spirit. She later got very sick and died

Patients referred to stories of people who had been "saved and they get cured" and reported that religious leaders' attitude towards condom use or ART was diverse, some supportive and some not. Traditional medicine is widely used in Kibera and some believe it can cure HIV or that HIV can be transmitted through bad spirits. Even those who expressed disbelief in traditional medicines, would still consider going to a traditional healer since traditional medicines were not associated with side effects and there are less demands attached compared to ART. A major reason, though, for not going to a traditional healer was high cost, as opposed to the ART that were distributed for free. A 23-year-old woman told us this story:

> So in my case, the traditional healer told me that I had crossed over bad water. He told me that if I agreed, he would pray for me. I wanted to go back but he asked for so much money I could not afford to go back (23-year-old female)

Illiteracy making patients unable to understand the information given by health workers
Most patients found the atmosphere at the MSF clinic professional and almost all felt comfortable, even if they wanted to keep their visits secret to others. However, a number of issues were brought up as possible barriers to treatment. The information given was sometimes experienced

as incomprehensible or frightening, discouraging patients to start on ART. They also felt the staff had too high expectations and demands on them. One woman described the visit at the clinic as follows:

> The only problem is that they do not have time to explain some of the information. Some people do not know how to read, yet they give us some pamphlets to read. You see, that is a bit complicated since you do not know how to read and you are expected to understand what is in the pamphlets before they give you the medication. It would be better if they could explain what is in the pamphlets so that one can understand (35-year-old female)

ADHERENCE TO ART

Determinants for low adherence to ART (Papers III, V)

Demographics

A total of 800 patients (mean age 37 years, 66% females) were included in the baseline assessment of Study V. The average household consisted of a widow who resided with 2-3 people excluding herself, with 2-3 biological children and supporting 4-5 people, sometimes outside the household. Seventy-five percent of the patients were living in Kibera, two-thirds of them for more than 5 years. Less than half of the patients (49%) had known their HIV status for over 2 years but most (83%) had disclosed it to someone. The mean time on ART was 23 (2-53) months. Only 40% of the respondents had a formal treatment buddy while 50% had friends or family members helping them to remember their medicines although a majority (60%) were satisfied with the support they received from family and friends. Thirty percent used alcohol, 8% had at least a unit of alcohol per day, while the majority, 70%, said they never consumed alcohol and only 0.6 % admitted to ever using any other drugs (heroin, marijuana, cocaine, khat or kuber).

Adherence outcomes

In Study III, the 830 patients started on ART received a total of 8 775 drug prescriptions (mean number of follow-up visits 11 ± 10 SD). Two hundred and twenty-one (27%) patients had an overall mean adherence below 95%. Among these, 65 (8% of 830) patients had a mean adherence below 80%. 70 (32%) patients with low adherence (overall adherence <95%) while in the programme later dropped out for more than 90 days after the last prescribed dose. In the logistic regression model assessing the association with low adherence, complete data were available for 825 patients and no factor remained independently associated with adherence.

In Study V, using dose adherence based on the number of missed doses over the last four days, 11% (n=33) of the patients were non-adherent (<95%) at six-month follow-up. The following variables were significantly associated with non-adherence in bivariate analysis: sex (female), undisclosed HIV status, not satisfied with support in taking ART medicines, low level of education, living below poverty limit (<US$ 2/day), short distance to clinic and short time on ART. In the final multivariate analysis, undisclosed HIV status (OR 4.70, 95% CI=1.78-12.43) and living below the poverty limit (OR 3.28, 95% CI=1.27-8.48) remained significantly associated with dose adherence <95%, also adjusting for age and sex.

When asked to report long-term adherence, 37% of the 352 patients said they had missed at least one of their ARV doses at some time between the past week and the last 3 months and as many as 15% had missed taking their ART last weekend. The most common stated reasons for missing drugs over the past month were "simply forgot" (28%) and "ran out of pills" (19%). According to the adherence index based on dose, timing and capacity to follow special drug instructions, 38% (130) of the patients were classified as non-adherent. The following variables were significantly associated with a low adherence index in bivariate analyses: undisclosed HIV status, not satisfied with support in taking ART, not having a treatment buddy, low level of education and unstable income. The following variables remained significantly associated with a low adherence index in the final multivariate analysis: not having a treatment buddy (OR 1.60, 95% CI=1.01-2.54) and low education (OR 1.95, 95% CI=1.21-3.15) also adjusted for age and sex.

DROP-OUT FROM ART

Missed appointments during civil strife (Paper II)

Our review of patient records from January 2008 in Paper II showed that 42% of 447 scheduled appointments were missed compared to only 14% in January 2007. This corresponds to more than 25% of all currently active ARV patients at the clinic. Twenty-five out of 63 (40%) staff responded to our questionnaire. The most common reason for absence from the clinic was fear of ethnic violence and a feeling of insecurity hindering both patients and staff from travelling back to Kibera after the Christmas holidays in rural homes. Several respondents stated they had been attacked by street gangs or ethnic mobs and had feared for their lives coming to the clinic which is centrally located in Kibera. All staff members said they had provided ARV to patients who normally go to other clinics, so it is not unlikely that some AMREF patients also obtained drugs at other clinics during the turbulence.

Reasons for drop-out from ART (Explorative phase, Paper IV)

(Corresponds to aim 3)

The AMREF clinic had noticed that a number of patients dropped out of the programme and did not return. Semi-structured interviews were conducted with 10 PLHIV (3 men, 7 women.) exploring reasons for dropping out of ART. Additionally focus group discussions were performed with 25 staff at the AMREF clinic. The reasons for dropping out of ART were influenced by the following factors:

- Religious beliefs
- Traditional medicine
- Lack of support from health staff
- Bad attitude from health staff
- Long waiting hours
- Food insufficiency
- Stigmatization in society
- Preservation of one's health and children's dependence on support

Support from health staff
The professional support from health staff personal (HSP) was addressed by several of the patients as an important factor for continuing taking the ARV as illustrated by this 43-year-old man:

> …there was an AMREF staff member who used to follow up on my treatment. She used to come to my house just to talk and advise me on how to carry on with life. She also reminded me that it was important to continue taking the medication.

Several of the PLHIV in the FGD expressed their gratitude for the support they received from the staff at the clinic. The work done by the counsellors was specifically mentioned as important, although some of the patients complained about the decline in access to counsellors, especially if you went to one of the satellite clinics outside Kibera.

On the contrary, lack of support was mentioned by some of the PLHIV as negatively influencing retention in care. Why these patients did not experience the same kind of support as the others was not revealed in the interviews.

Bad attitude from staff
The negative attitude among some of the HSP was raised by PLHIV in the FGD as sometimes being a barrier for retention in the programme.

> The attendants took my file and hid it so that the doctor could not see it. At 12.00 I went in the consultation room and asked the doctor if he could see me but he said that he did not have my file. At 1 pm I went and asked the attendant if she had my file but she asked me not to talk to her. I went back to my house, had lunch and then went back to the clinic and told a social worker and explained the situation to him. He looked but he did not find it. When the attendant saw the social worker looking for my file, she went and got it from where she had hidden it and took it to the consultation room. The doctor then attended to me that afternoon. That incident made me not want to go to the clinic anymore because the attendant did not like me and she always frustrated me. (Woman, 43 years old.)

One of the PLHIV, who had dropped out, simply went to another hospital to get treated after having tried to explain for a clinical officer at the AMREF clinic for over one year about her chronic cough that did not disappear. Another PLHIV said the clinical officers were harsh and favoured the patients already known to them. In one of the FGDs it was brought to our attention that the COs often rotate from one clinic to another, thus patients often met different COs, not experiencing any continuity of care. Also - as told by a CHW in one of the FGD – some of the patients seem to fear the doctors at the clinic, not being able to freely talk about their problems.

Long waiting hours
Both patients and health staff personal (HSP) discussed long waiting hours as a barrier to retention in programme.

> Sometimes having not had breakfast, it would be difficult for me to wait for long so I got angry and stopped taking the ARV (26-year-old woman).

One often stated reason for long waiting hours was the handling of files. This was perceived as disorganized. Many files were lost or took a long time to find. Since the AMREF clinic is an integrated clinic, with both HIV- and non-HIV patients, the work load for the clinicians is often hard, which was raised by the COs as an explanation as to why sometimes the waiting times can be long. The combination of long waiting hours and not understanding the waiting system led to unnecessary frustration for some patients.

Food insufficiency
Most patients reported lack of food being one of the main barriers to continuing ARV medication. They described how they are getting hungrier when taking the ARV but at the same time cannot afford to buy food.

> When one is using ARV, they need to eat. So if one has no food, the ARV are too strong for them. You will find that sometimes people will skip taking the ARV for a day because they have no food and when one resumes, the side effects are quite serious. All this is because they have no food. (39-year old woman)

Or, as a clinical officer in a FGD put it: "The priority for people in Kibera is not health but how and where they will get the next meal." The FGDs with PLHIV and CHWs confirmed that the vast poverty was the main concern for many patients. Some of the CHWs claimed that a comprehensive ARV programme should include a supplementary food programme, as was the case for some other NGOs in the area.

Stigmatization in community
In the Kibera community where people live close to their neighbours, stigmatization was described by many patients as widespread and hard to challenge. The stigma often makes it hard for people to take ARV, as this 28-year-old woman put it:

> I would have stopped (ARV) but luckily my landlord made a place for me so that I was not interacting much with my neighbours. If I had continued interacting with my neighbours on a daily basis, I would have lost hope and given up. This is because they kept saying that I would die soon.

HSP and CHWs requested more awareness campaigns to fight stigma and misconceptions. PLHIV in the FGD said the key to overcome stigma is through post-test clubs and support group meetings where the PLHIV themselves should be more active since they are the ones most enlightened and updated on the issues of stigma and discrimination.

Stigmatization made it hard for many patients to disclose their status. Disclosure was therefore expressed by several participants in the FGDs as an important barrier to ARV-treatment. One woman in the key informant interview told about her friend who had been lying to her husband, who had not been tested, about the ARV she took, saying they were vitamins. He got angry, for no obvious reason, and threw the pills away. Since then, the friend feared going back to the clinic to ask for more medicines and has therefore dropped out. The constant hiding of one's pills, as stated by PLHIV, could be overcome by encouraging people to disclose to spouse or friends. More home-visits should be made to those who have not disclosed, according to the CHW.

Religious beliefs

Religious beliefs are important for many patients in the Kibera society, according to the PLHIV. As a result, many explained that they lay their decisions in the hands of God. At the same time they seemed to accept the taking of ARVs as a necessity. The religious belief and the acceptance of ARV appear to be integrated in the patient's minds.

> Now that I am back on ARV, I do not think that I will stop. I have decided that I will use ARV until the day God will save me. If there will be need for me to stop using the ARV, I believe that God will talk to me directly. I cannot stop taking the ARV because of any other reason, I have learnt from my previous experience. (Woman in FGD)

For others, religious belief was the main reason when deciding to discontinue treatment. PLHIV and CHWs reported having heard pastors preaching about how one can get cured through healing instead of taking ARV:

> There were some women with whom I used to get ARV at the AMREF clinic. They came and told me that they had been prayed for and they were no longer using ARV, yet they were ok. They actually looked healthier than me. So I decided that I would also go to the same people that prayed for my friends. You know the Bible says faith can cause one to get healed. Since I am a born-again Christian, I believed that I was healed once I was prayed for. (42-year old woman)

Several of the PLHIV explained that they believed that they can get healed by intense praying, but, at the same time, they expressed the importance of taking ARV. When discussing these issues it became clear that these two worlds – faith versus ARV – sometimes contradict each other, sometimes not. Some of the PLHIV wanted, in the future, to get tested again and were hoping for a negative result after being healed. Even then, when asked if they would at that point stop taking ARV, the answer was no: They would still continue treatment.

Traditional medicine

The use of TM was described by most interviewees as widespread in Kibera and many patients seemed to balance between their conceptions of TM and ARV:

> I would hate to be as sick as I was before I started using ARV. I would however try alternative medicine if there is proof that it can cure me. (49-year old man)

Although almost all PLHIV had tried herbal medicines before they expressed different views on the efficacy of TM and as a result to this many seemed ambivalent about herbal medicines. Several patients thought TM was less associated with side-effects than ARV. Therefore, in some cases, there was a sense of understanding for patients who preferred TM over ARV.

Preservation of one's health and children's dependence on support

Further, the preservation of one's health and the responsibility for taking care of one's family were mentioned as important factors for taking the ARV.

> I know the ARV are good because they boost my immunity. I know with ARV I can manage to raise my children and can be strong enough to work. So I do not think that the ARV are bad in any way. (49-year old woman)

Reasons for dropping out of ART related to traditional medicine and religion (Paper IV)

Four main categories were revealed in the interviews for Paper IV as reasons for discontinuing ART:

- Patients' firm belief in traditional medicine compared to biomedical medicine
- Faith, praying and religious practices
- Attitudes from church/pastor
- Trigger events

The 20 interviewees described a decisional process prior to the actual discontinuation from the ART programme that involved a trigger event, i.e. a specific event that influenced them to make the actual decision to stop ART. All patients were living in extremely poor conditions, struggling to find food, overcoming stigma and finding it difficult to disclose their status. Many had been diagnosed with HIV at a late stage, often already showing signs of AIDS. Several of the women were widows. Their husbands had, in many cases, died of AIDS. The husbands had often started ART too late or completely refused treatment at the beginning. TM and religion were key elements in all the interviewees' lives and continued to be so also after ART initiation. An important aspect was the fact that TM and religion were perceived as factors that the patient could control while many other events that the patients experienced during the process from ART-initiation to discontinuation were perceived to be beyond their individual control, as presented in the conceptual framework (Figure 7). Another important finding was that TM was related to cure and religion was linked to the possibility of getting healed. Both cure and healing we interpreted as the same as getting free from the HIV.

All patients were living under extremely poor conditions, struggling to find food, overcoming stigma and finding it difficult to disclose their status. Many had been diagnosed with HIV at a late stage, often already showing signs of AIDS. Several of the women were widows and in many cases their husbands had died of AIDS having started ART too late or completely refused treatment at the time of diagnosis. Traditional medicine and religion were key elements in all the interviewees' lives even before being HIV positive and continued to be so also after ART initiation. An important aspect was the fact that the use of traditional medicine, prayers and other religious practices were perceived as factors that the patient could control as compared to many other factors that patients experienced during ART that were perceived to be beyond their individual control, as presented in the conceptual framework (Figure 7). Another important finding was that in the minds of the patients, traditional medicine was related to cure and religion was linked to the possibility of getting healed. Both cure and healing were interpreted as the eradication of HIV infection.

Patients' firm belief in traditional medicine compared to biomedical medicine

The possibility of getting cured by taking traditional medicine was raised as a reason for taking traditional medicine instead of ART.

> If you use them (herbs) properly there is a possibility of getting cured … According to what I have heard about the ART it is possible that the viral load might be undetectable but still the virus will be in the body. (P 2)

The patients described traditional medicine as something within their own control, something they could choose to take or not. Many patients had taken traditional medicine or sought a traditional health practitioner for care since childhood and this was their usual way of seeking health care.

None of the patients interviewed in this study felt they could discuss traditional medicine openly with the staff at the AMREF clinic. The staff told the patients to never mix ART and traditional medicine and this message was well known to all interviewees.

On the other hand, most respondents described how they were strongly encouraged to take traditional medicine by family members or friends.

> I was living with my grandmother who is a herbalist. She told me to use the herbs because they are safer than the other medicine. She said the ART have chemicals that affect the body but the herbs are natural. (P 5)

Some of the interviewees were even forced by family members to stop ART and start traditional medicine.

> My mother forced me to use the traditional medicine ... She just told me to use the traditional medicine because it is good ... She told me that she gives the herbs to other people and they get well ... I told her that I was using ART but she told me to stop and use the herbs. (P 6)

The patients thus had to make one out of three possible decisions: continue taking ART and ignore traditional medicine; take traditional medicine and stop ART; or take both at once.

None of the respondents had revealed their use of traditional medicine to the health care staff at the HIV clinic.

Faith, praying and religious practices

Religious practices were described at two levels: one personal, related to the amount of praying, and, a second more formal level, linked to religious rituals and visits to different religious institutions. Both of these levels were perceived as being within the control of the patient. Many respondents had a firm belief in God's power to heal them and get rid of the disease. Even patients with deteriorating health often believed that if they prayed more and had more faith in God, they would eventually be guided and helped.

> Even if one uses medication but they do not believe in God they cannot get well. I believe that God is capable of healing any person whether they are using medication or not. I would rather believe in God and go on with my life and take care of my children … Prayer only is enough. When I was very sick I was prayed for and I even got better before I started taking ART. Even if I did go to hospital, I believe that the prayers helped. Even those that pray go to hospital. (P1)

Many interviewees seemed to doubt the effect of ART while they strongly believed in prayers. These patients often referred to stories they had heard or people they knew who had bad experiences of ART:

> I stopped using the ART because of prayers. Also because I have two other friends that are HIV-infected but one died yet she was using ART, I do not know what was wrong that made her die. I am not using ART, I just pray and I am alive and well. (P 11)

Attitudes from church/pastor

Since almost all the patients in our study reported going to church or a mosque regularly, the influence of pastors/imams and church/mosque elders was of great importance when facing the challenges surrounding HIV and ART. Some patients expressed fear of the priests' reaction to them being HIV infected.

> I have not disclosed to any priest because they always come and go. They are usually transferred; they are not permanent. There are some church elders but they are not that perfect. You may tell them, but they may end up announcing it to the church or to other people. Even with the priest you have to weigh your options and see if he can keep your secret and then you can disclose to him. (P 14)

Some of the interviewees had seen fellow members of the church being expelled after disclosing their status. The ones that had disclosed their status had sometimes faced negative reactions from pastors and church elders and some had even been forced to leave their congregations.

Trigger events

Almost all patients described an event that made them decide to stop ART. Often it was meeting with a person who influenced them to discontinue the ART.

> He (a friend) was also HIV positive and so when he was taking the traditional medicine and saw the changes, he told me. So he is the one who made me stop taking the ART because I saw the changes and he was much better and healthier than before. (P 18)

The trigger event was often a religious event, for instance a prayer meeting:

> They said that those who are infected with HIV are healed. They also said that those who were in that meeting and were using the ART should stop because they are healed. (P 13)

Often a friend who had positive experiences from praying inspired the patients to discontinue ART.

> I saw a friend of mine who had gone for prayers somewhere. She explained to me and asked me to go for prayers with her. I followed her and I saw people who were being prayed for and they even stopped using ART. I then decided to do as they were doing. (P 9)

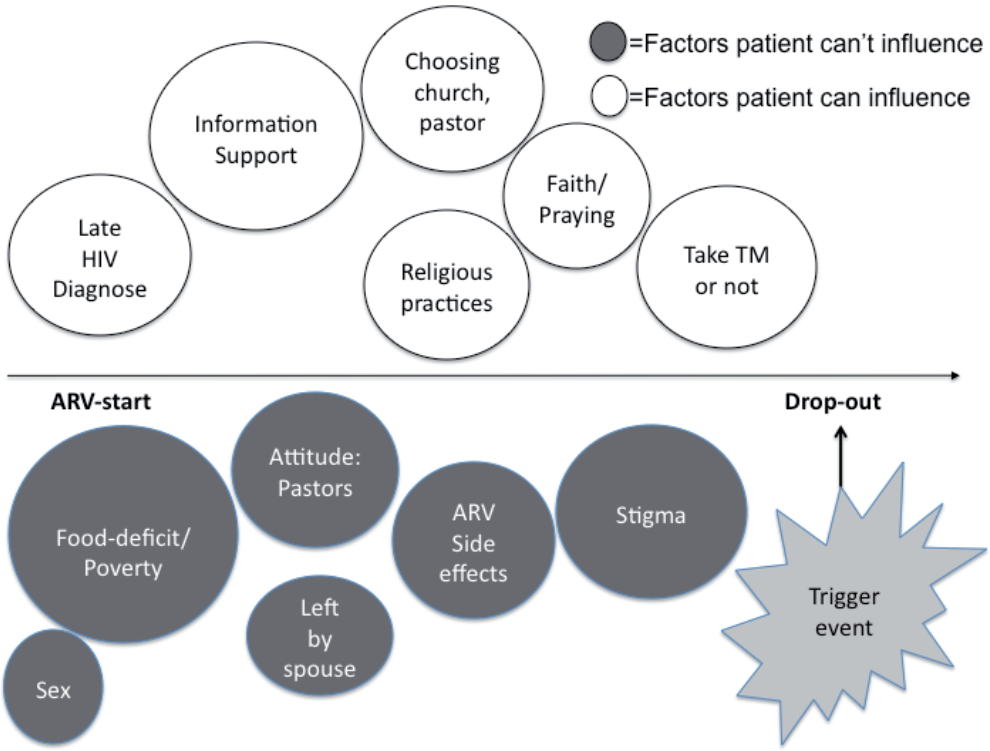

Figure 7. *Factors that the patients perceived that they could influence and not influence according to the interviews in Study IV.*

Determinants for drop-out from ART (Papers III, V)

Two hundred and forty-four (29%) patients out of the 830 patients in the retrospective Paper III that were started on ART dropped out of the programme for more than 90 days after the last prescribed dose. The corresponding drop-out rate was 23 per 100 person-years. For drop-out patients the mean time on ART was 257 days and for non-drop-out patients the mean time on ART was 549 days ($P<0.01$). Complete data was available for 648 patients in the logistic regression model. Sex, age, duration on ART, clinical status on ART-initiation, choice of ART-regime, concurrent tuberculosis disease and weight at ART-initiation were included in the logistic regression model as independent variables. Residence in Kibera (OR = 11.1, 95% CI: 5.9 to 21.1; P < 0.001) was the only factor significantly associated with drop-out. The Kaplan-Meier probability of remaining on care and treatment was 0.83 at 6 months (95% CI 0.81-0.84), 0.74 at 12 months (95% CI 0.67-0.76) and 0.65 at 24 months (95% CI 0.63-0.67).

Out of the 800 patients on ART included in the baseline assessment of the prospective Paper V, 101 patients were excluded from the survival analysis due to missing data on appointment dates and number of doses prescribed. Out of the 699 patients included in the analysis, 163 (23%) dropped out for more than 90 days after last prescribed dose, leaving 536 (77 %) in the ART programme at the end of the study. The total number of clinic appointment years of follow-up was 1 828. The Cox regression model showed a significantly higher hazard ratio for people not having a treatment buddy (HR 1.41, 95% CI=1.02-1.94), adjusted for age and sex.

Table 8. Overview of study results by paper

Study:	**I**	**II**	**III**	**IV explorative**	**IV**	**V**
Aim:	Reasons for non-uptake of ART	Access to ARV during conflict	Levels of drop-out and adherence	Reasons for drop-out from ART program	Traditional medicine and religion and drop-out	Levels of drop-out and adherence
Type of study:	(Qualitative study)	(Quantitative study)	(Quantitative study)	(Qualitative study)	(Qualitative study)	(Quantitative study)
Results:	Lack of food Side-effects Disclosure and repercussion Continuity of treatment Alternative care Illiteracy	42% missed appointments compared to 14% previous year Fear of ethnic violence Feeling of insecurity	830 patients Adherence<95%: 27% Adherence<80%: 8% Drop-out>90 days: 29% Drop-out associated with Kibera resident Probability remaining in care: 6 months: 0.83 12 months: 0.74 18 months: 0.65	Religious beliefs Traditional medicine Lack of support Bad attitude from health staff Long waiting hours Food insufficiency Stigma in society Preservation of one's health	Belief in TM compared to biomedical medicine Faith, praying and religious practices Attitudes from church/pastor Trigger event	800 patients Dose-adherence<95%. 11% Non-disclosure Poverty Non-adherent adherence-index: 38% No treatment buddy Low education Drop-out>90 days: 23% No treatment buddy

DISCUSSION

GENERAL DISCUSSION ON FINDINGS

The main reason for not accepting ART in the first study was fear of taking medication on an empty stomach due to lack of food. In Study II one fourth of ART patients had a low adherence but no factor remained independently associated with low adherence. Almost one third dropped out of the programme and residence in Kibera was associated with drop-out. As shown in Study IV the most important reasons for dropping-out from ART that were related to religious beliefs and traditional medicine were: patients' firm belief that traditional medicine was more effective/ had fewer side effects compared to biomedical medicine; faith, praying and religious practices to seek a cure from HIV; negative attitudes from religious leaders; and; important personal trigger events. Among 800 patients in Study V, undisclosed HIV-status, living below the poverty limit, lack of treatment buddy and low education were significant predictors of low adherence. Almost 1 in 4 dropped-out from the ART programme and Cox regression analyses showed a significantly higher hazard ratio for people who lacked a treatment buddy for support.

Uptake of ART

Late initiation of ART in many low-income countries is a major factor for early AIDS-related mortality [101]. Patients are forced to accept their HIV diagnosis at the same time as they must reveal their status and cope with the idea of life-long treatment. This is probably an important reason for delayed uptake or non-acceptance of ART in resource-poor settings like the Kibera slum. However, many of the interviewees in our Study I that refused ART knew that they needed these drugs to survive, but lacked the strength to overcome existing barriers such as unemployment, poverty and stigma. Feasible tools to assess readiness for treatment are thus needed [138, 199, 200].

It would be ideal if readiness could be checked for all patients before starting ART, as recommended by the international AIDS Society-USA Panel [201]. Many of the theories on readiness have several components in common. First, the patient is unaware of the need for change of the undesirable behaviour (e.g. non-adherence to ART) since patients are often in a crisis state of mind at this early phase after having received the HIV-diagnosis. After this, the patient often enters a period of weighing advantages and disadvantages of the wanted change in life (taking ART). At this stage, trigger events or cues play a significant role, i.e. something must now happen in order for the patient to take the decision to make the change, something that makes the pros outweigh the cons. In this process the patient first adapts and then makes the proper changes in life in order to prepare for this action to happen (i.e. find the clinic, support groups etc). Only after this process is the patient ready to accept a change in life (e.g. initiating ART) [132, 133, 137]. All these steps take place under what can be called "normal" circumstances according to the readiness theories. The difference in many SSA settings like Kibera is that the patients do not have time to weigh advantages and disadvantages given the common delays in care-seeking. They are told to start ART at a few days', or weeks', notice since their CD4 count is so low or their physical status is deteriorated.

Poverty dominates people's life in urban slums like Kibera, regardless of HIV status. Lack of food and a perceived risk associated with taking ART on an empty stomach was the most important obstacle to starting ART as stated by the interviewees in Study I. Like most other ART programmes, the MSF clinic in Kibera did not include food provision at the time of study, but patients were informed to eat well to avoid side-effects and for the drugs to be efficient. Addressing the issue of food security and understanding the depth of poverty in settings where ART programmes are introduced remains critical for successful initiation of sustainable ART. It is important to find vulnerable groups of patients that are known to refuse ART and to enforce special support for those patients.

The majority of the patients in Study I were afraid of the side effects associated with ART. Many misinterpreted the death of family members as caused by the medication rather than by AIDS or opportunistic infections. Coping with the initial side effects of ART requires a well-informed client, which is more challenging to achieve in contexts where illiteracy and lack of health staff is a reality [85]. Information about side effects was given orally by health workers and by handing out pamphlets. However, most patients interviewed had no or very basic education and were too embarrassed to reveal their illiteracy and ask for help. To increase the uptake of ART and to maintain high adherence, health information needs to be communicated through different channels, for example, based on patients' suggestions, by peers informing each other on how to cope with side effects [202, 203].

Several of the interviewees in Study I had not disclosed their HIV status to their spouse out of fear of being left alone or getting beaten. There are gender differences in HIV disclosure in SSA and women fear physical violence while men are more concerned about their status being exposed [204]. It has been shown that intimate partner violence is associated with an increased incidence of HIV infection [205] and in some SSA countries up to 50% of women experience domestic violence during their lifetime [206, 207]. Some of the women in our study (I) were afraid of disclosing to their spouse since he could be upset and even harm them. It is essential to strengthen prevention of partner violence in settings like Kibera in order to make it possible for women to start ARV treatment.

Our findings from Study I indicate that ART providers must also become more aware of the crucial importance of religion and traditional medicine in patients' decision-making regarding ART and address these issues in a non-judgemental way. Although our respondents expressed ambivalence about alternative medicine, many had sought help from traditional healers. Many were also grateful for the support they had received from the church but some respondents were sceptical about the attitudes among religious leaders towards ART and safe sex. Some felt confused after religious figures had asked them to perform rituals in order to get rid of the virus or to be relieved from symptoms.

Adherence to ART

Low adherence to ART is one of the most important predictors of disease progression and AIDS [122, 123, 208]. The level of adherence required to avoid development of resistance has been debated over the past ten years since Paterson et al (2000) claimed that a 95% adherence to ART was necessary [117]. Later researchers have argued that lower adherence levels may be sufficient to sustain viral suppression [114, 209].

Most patients (99%) in our Studies III and V from the AMREF clinic were receiving NRTI and NNRTI, not PIs. NRTI and NNRTI type drugs are more linked to development of resistance following periods of treatment interruption (> 1 week) but findings from studies performed in high-income countries with newer ART drugs cannot always be compared with studies performed in SSA since newer drugs and second line treatments are much more rare in SSA.

In the retrospective Study III more than one quarter (27%) of the patients had an overall adherence below 95% and 8% of the total had a mean adherence below 80%. In the prospective Study V, 11% of the patients were non-adherent according to the dose adherence calculations based on the self-reported number of pills missed during the last four days. The adherence index created, taking into account timing and special instructions, showed an adherence of 38%. In the multivariate logistic regression (Study V), not disclosing HIV status and not having a formal treatment buddy were significant predictors for non-adherence. This is in line with a number of other studies on adherence also showing that social support and disclosure are important facilitators for adherence [169, 170, 173]. In a context like the Kibera slum, disclosing HIV status can be linked with great challenges since people in the slum often share small houses and hiding one's status and/or pills can be difficult [105, 210].

Furthermore, living below the poverty limit and low education were associated with non-adherence. As pointed out by Weiser et al (2010) food insecurity is a major obstacle to ART adherence [176] and was also a barrier for uptake of ART as we showed in Study I. The poverty – and associated food insecurity – in the Kibera slum is perhaps the main cause of drop-out and the main challenge to uptake [105] and sustainable adherence faced by health care providers in Kibera. It is difficult to see how this can be solved other than pointing out that people need a more stable income to provide food for their families.

Choice of method for measuring adherence and drop-out

There is no consensus on which adherence measures to use [139]. Methods include indirect measures (e.g. pill counts, self-reports, electronic monitoring devices and medication refill rates) [117, 140, 141] and direct measures (e.g. observations, drug monitoring and biological markers) [142]. Self-reported measures are quick and inexpensive [143], have been shown to predict clinical outcome [144] and have a significant association with viral load [143]. However, self-reports and pill counts tend to overestimate adherence [144, 145], while medication refill rates need electronic pharmacy data systems in order to be efficient and these are not common in sub-Saharan Africa [109].

We used the CSA to estimate adherence in Study III, which is based on actual prescriptions and days between drug refills [148, 152]. The CSA does not give information on actual drug intake, but provides convenient, non-invasive, objective, and inexpensive estimates of the highest possible level of drug intake, which will generate a conservative estimate of low adherence [148]. It is also the preferred method for calculating adherence from administrative data when there is high attrition [148], which was the case in our retrospective study (29% drop-out).

The fact that the proportion of patients classified as non-adherent in Study V increased from 11% to 38% depending on the type of adherence measure used (i.e. dose adherence versus adherence index) indicates that patients often are classified as being adherent when only the number of

missed pills during the last few days are assessed. Thus, it is important to view adherence as multi-factorial and to assess different aspects including dose timing and capacity to follow food restrictions, in order to achieve virologic suppression [99, 100]. However, the importance of following exact schedules and food instructions is dependant on the type of drug combination and of special concern for patients on protease inhibitors (PIs) [211, 212]. Although in the present cohort only 0.8% of the patients were on a PI-based regimen, some nucleoside reverse transcriptase inhibitors (NRTIs) (e.g. didanosine) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) (e.g. efavirenz), both frequently used antiretrovirals at the AMREF clinic, are also associated with food restrictions [73]. In the cohort of Study V, 38% of the patients had a low adherence index score assessing timing and special instructions in addition to dosing. This is in line with earlier studies from other resource-poor African settings where 47-78% of patients are categorized as adherent when dosing, timing and food instructions are taken into account [99, 173, 213].

While considering that we found varying adherence levels between 11%-38%, depending on what method was used in the different studies, we can only speculate on the "real" adherence level. Several of our methods include self-reports that could overestimate adherence. The aim when choosing an adherence method is to find a simple, cheap method that can be used by health staff, already under considerable time pressure. We conclude that the self-reported adherence index used in Study V is easy to use, does not take much time to perform and captures patients with low adherence when the important aspects of timing and special instructions are included.

Drop-out from ART

The number of patients discontinuing treatment in SSA is unknown but thought to be substantial [32, 214]. In a review of 33 cohorts in SSA, including a total of 74 192 patients in 13 countries, Rosen et al (2007) demonstrated similar results. ART programmes in SSA had mean retention rates of 79%, 75% and 62% at 6, 12 and 24 months respectively and the range of reported total retention varied between 39% and 90% [153]. There are specific challenges to sustaining HIV care and treatment programmes in informal settlements in SSA given the high mobility, poverty, lack of family support structures, mixed target populations and higher risk behaviours including alcohol and drug use in the populations residing there. Previously, little research has been conducted on retention in care in SSA informal settings which are addressing these challenges but several authorities in this field of research have demanded more context-specific studies [163, 164, 169].

Measuring drop-out rates may be problematic especially in informal settings where indivudal patients are difficult to trace due to high mobility and lack specific contact details, but also out of respect for individual integrity and to avoid a breach of confidentiality. Due to the retrospective nature of Study III we were not able to classify reasons for drop-out, while in Study V we managed to retrieve more accurate follow-up information on drop-out that could be linked to baseline data, and also enabled the interviewer to validate patient drop-outs directly with the staff while these patients were still fresh in memory. We opted for a conservative definition of drop-out, using an interval as long as 90 days so as not to over-estimate the drop-out risk in both Study III and V.

A substantial number of patients (29% in Study III and 23% in Study V) dropped out for more than 90 days, and hence stayed without treatment for time periods that placed them at risk for developing opportunistic infections, deteriorating health and premature death [101, 208]. Kibera residents had an eleven-times higher risk than non-Kibera residents, of dropping-out in Study III. The harsh conditions associated with living in an urban slum like Kibera are likely to be related to this risk elevation, and may include underlying causes of drop-out such as premature death, competing causes of disease, alcohol or substance abuse, poverty and high mobility. Kibera residents have usually migrated from the countryside, and the need to travel may partly contribute to their much higher risk of drop-out. One way of handling patients' need to travel is to systematically dispense drugs for longer periods of time, but the disadvantages include drugs being lost or sold, and the patient being away from the support structure for a longer period of time. Scanty evidence exists on the possibilities of accessing ART in other geographical areas. Buying ART from a private provider or on the black market is associated with high costs, which probably restricts this possibility for Kibera residents (Personal communication AMREF, September 2008).

In Study V the Cox regression model showed a significantly higher hazard ratio for people not having a treatment buddy to drop out of the ART programme (HR 1.41, 95% CI=1.02-1.94), adjusted for age and sex. Social support has been shown to be a strong supportive factor for retention in programmes in other SSA settings [59, 177].

More than 4 in 10 HIV patients were likely to have experienced treatment interruption lasting for several weeks after the violence following the elections in 2007/08, as shown in Study II. Since many patients in this context seek care late with low CD4 counts, treatment interruptions may rapidly lead to AIDS symptoms and deteriorating health, especially for patients who recently have been initiated on ART. Also, since 99% (data not shown) of the patients were only taking NRTI and NNRTI, even short periods of irregular drug intake may lead to development of drug resistance [215, 216], which is especially problematic where second or third line ARV are not affordable. Studies from SSA have shown that adherence levels of 68-85% can be achieved [217] but weak health systems, staff shortages and stigma all contribute to jeopardizing regular drug intake and patient retention in ARV programmes [169, 218].

The objective of Study IV was to explore the influence of traditional medicine and religion on discontinuation of ART in an informal urban settlement. Traditional medicine has previously been found to be an important factor for low adherence to ART in many African countries [163] but to our knowledge the relationship between traditional medicine/religion and treatment discontinuation has not been studied. The interviews in Study IV showed that many of the interviewees believed that traditional medicine and/or religion would cure the HIV infection, while ART, at best, would only prolong life. Some even thought that ART could cause premature death. Most patients reported having tried traditional medicine to get cured from HIV. At the same time, many seemed to know that herbal medicines are less efficient than ART in fighting HIV and that they should not be mixed. Counselling patients to not mix ART and traditional medicine appeared to be contra-productive in this setting. Patients used to taking traditional medicine since childhood might switch from ART to traditional medicine when experiencing side-effects or when opportunistic infections occur. These treatment interruptions, not supervised by trained health professionals, could lead to development of resistance due to half-life differences of antiretroviral drugs. The treatment interruptions we noted as a result of the 'do-not-mix' message

could be a more serious threat to public health than possible, but yet unknown, drug interactions between ART and the traditional medicine used in the Kibera slum. When treating, or counselling patients for any disease, it is important to take the widespread use of traditional medicine into account [219, 220]. Since all the patients interviewed in this study felt they could not discuss traditional medicine with the staff at the clinic, the importance of open discussions regarding this topic cannot be over-emphasized.

Many interviewees in Study IV stopped ART and took up praying instead since, as they expressed it, they saw a chance of getting healed through God. When struggling with the challenges related to ART, such as side-effects, enhanced feelings of hunger, and stigma, many chose, as they said, to put their lives in the hands of God, trusting he would make them better or even cure them of the HIV infection. Since religion is such an important part of many patients' lives, religious discussions should be included in the day-to-day work of the clinic. Another key issue in this setting is discussion with church representatives about the effects of negative attitudes towards positive HIV status and the importance of taking the ART.

As shown in the conceptual framework (Figure 7), according to the interviewees in Study IV the process from ART initiation to discontinuation was influenced by numerous factors. These could be divided into factors within the patient's control and factors that were perceived as outside the control of the patient. Several factors, like a shortage of food or the ART side-effects were perceived by the patients as being outside their control. On the other hand, the decision as to which church to attend or which ARV clinic to choose, lies within the control of the patient. According to the patients in this study, they needed to somehow get control of their lives before being committed to adhering to the ARV treatment and to stay in the programme, something that can be challenging when living in a difficult context like this.

This need for control to increase adherence has been previously shown in other studies [137, 221]. Interventions to decrease discontinuation of ART need to focus on the factors that the individual can control, such as the time of diagnosis, by encouraging people to get tested for HIV. Patients initiating treatment should be informed about the possible side effects they could experience. There is also need to influence attitudes towards ART in the community so that patients understand that initiating ART treatment too late may result in the treatment not being effective. It is important to review the information provided at the clinic concerning traditional medicine, as well as encouraging an open dialogue about religious issues.

METHODOLOGICAL CONSIDERATIONS

Strength of studies

One strength of the studies in this thesis was that they were unique in their kind, conducted in an urban slum which is a very complex study area with around 500 000 – 1 000 000, highly mobile, people of more than 40 ethnic backgrounds, all confined to living in an area as small as Central Park in New York. Nevertheless, this environment is similar to what many patients in need of ART face globally today. Logistic challenges to perform studies in this environment are substantial, yet interesting findings were revealed in collaboration with our collaborators at MSF and AMREF. Due to security reasons we could not walk to the clinic without being accompanied by someone from the staff, nor could we stay in the slum after nightfall. Despite these restraints we managed to interview patients in their homes.

The longitudinal cohort designs used in Studies III and V enabled us to study drop-out rates in relation to time. Compared to the retrospective design in Study III, the prospective nature of Study V has methodological advantages including higher reliability and validity provided by the well-controlled data collection, where we were able to retrieve direct adherence information from the patients, who provided us with detailed information at follow-up interviews, information that could be linked to baseline data. Additionally, the prospective design enabled the interviewer to validate the accuracy of patient drop-outs directly with the staff, while these patients were fresh in their memory.

We performed a quality check on the data entry for Study V (January 2009) and this revealed a high level of consistency when comparing the baseline and follow-up questionnaires with the data entry, which had been carried out by the research assistant. Twenty baseline and 10 follow-up questionnaires were randomly checked for data entry errors, including 2 040 and 680 items (baseline and follow-up) respectively. Out of 2 720 items checked we found 7+1 (baseline and follow-up) errors, hence a very low error rate of 8/2720 = 0.29%.

Another strength was that we were able to trace some of the drop-outs from the ART programme and to interview them about their reasons for doing so. In Study IV, both for the explorative phase as well as for the more in-depth part about traditional medicine and religion, we managed to identify patients who had dropped out of ART and approach them for interview.

Lastly, all studies have been performed in the same setting enabling us to gain a deeper understanding of the context, the patients and the research questions. We have been able to pose a question, get back to the clinic many times and, step-by-step, gain more and more knowledge about the setting.

Limitations of studies

Information bias

One limitation of Studies III and V was the amount of missing data, caused by a number of factors. Data on clinic appointment dates and number of prescribed doses, for example, were missing for many patients, mainly due to inconsistencies in outpatient numbers and/or clinic appointment dates. Some variables had missing data since the patients did not want to answer the questions or had problems with formulating a response. Further, information on what happened to the drop-outs in Study V was not available although efforts were made to trace these drop-outs with the help of community health workers. A few variables included in the statistical modelling (time in Kibera, time since ART initiation, income level, having had another previous ART provider or being hospitalized due to AIDS) had a substantial amount of missing values and further analyses were therefore performed to assess the potential of non-random bias. The hypothesis that our data was missing completely at random (MCAR) was also statistically verified using Little´s MCAR test (p-value equal to 0.259) rejecting any systemic bias in terms of missing data. In conclusion, the likelihood is low that the missing values could have biased our results away from the null hypothesis.

The most frequent comparative measure in adherence studies are pill count and Medical Event Monitoring System (MEMS) [117]. Due to economic restraints we did not have any other comparative adherence measurements.

In most studies on adherence to ART basic laboratory data are available, like CD4 count and viral load. Since the studies for this thesis were performed with the ambition of not interfering with the regular clinical work in any extensive way, we accepted the existing set up and did not make any changes in the daily routines at the clinic. This included the fact that viral load was almost never measured due to financial restraints at the clinic. Only in exceptional cases, where patients showed major problems with treatment failure, were viral load and resistance testing performed as in most clinical settings providing ART in SSA. And even though CD4 count was supposed to have been done for all patients at study start according to the AMREF clinic's own guidelines, we only found available data on CD4 counts for about one quarter of the patients (Study III). This could have been due to inadequate data entry, but more likely it was due to the reality in many SSA contexts, where clinical care is provided out of necessity in spite of resource constraints.

There was an obvious under-reporting in the number of patients claiming to use alcohol or other drugs in Study V. According to the staff at the clinic this was due to the shame and guilt related to alcohol use in the community.

Social desirability in the interview Studies I and IV could have influenced the respondents to say things they believed the interviewer wanted to hear. However, measures were taken to limit the risk of such bias. None of the persons carrying out the interviews were MSF or AMREF staff and since negative comments were made about both the evaluated ART programmes we believe social desirability was limited.

Sampling
In qualitative research the sample is often small and purposeful [222]. In Studies I and IV new patients were sought for interviews until saturation of the material was reached. An interview guide was used with a number of questions that were adjusted and added to after about half of the interviews when other categories of questions were revealed. For the quantitative Studies III and V, all patients were included that were enrolled that the AMREF clinic.

Selection bias
In the prospective cohort the patients did not receive any incentives and the interviews did not take much time. All patients coming to the clinic were asked to participate. The reason so few men were interviewed in Study IV was partly a reflection of reality since the ratio of women to men followed at the clinic was 2:1. Another possible reason though was that women were more motivated to participate, according to the CHWs. The selection of patients reporting adherence data in Study V reflected those who were included in the programme at the point of baseline and at follow-up, and might be biased in comparison to drop-outs, with potentially under-estimated levels of non-adherence as a consequence.

In the prospective cohort study (V), we found that about 3% of the patients were Muslims. The exact number of Muslims in Kibera is not known but several mosques and imams are active in the area. Even as early as Study I we aimed to interview patients with different ethnic backgrounds as well as belonging to different religions, but no Muslim patient agreed to be interviewed even after being approached several times. The reason for this is unknown and this remains a limitation to our studies. Nor did we interview more than one traditional healer and one herbalist but focused exclusively on the patients' views, something which may also be considered as a weakness.

Reflexivity

It is important to be aware of one's own stand as a researcher and how class, gender and age affect the research process. Reflexivity refers to the way that knowledge is shaped by these factors and how the role of the researcher is taken into consideration during the research process [223]. When arriving in Kibera there were a number of challenges to overcome. The security issue regarding spending time in the slum was, at first, slightly stressful. But thanks to our research assistant and a local PLHIV who helped us to find our way around Kibera, this feeling of insecurity decreased. To depend on a translator for almost every contact with the patients was another factor that took some time to accept. At the same time, as a newcomer, I was allowed to ask many naïve questions about the Kibera slum and the people living there.

Being a western, white, foreign, male doctor interviewing mostly women could have been an obvious obstacle to gaining trust from the patients. I tried to make it clear to the patients that I was not part of the staff at the clinic and that I did not have anything to do with the treatment of patients, and that nothing they said to me would affect their treatment at the clinic. I was told by the PLHIV who worked as volunteers at the clinic and who guided us around that they did not think that the patients were under any additional stress due to the fact that I was a foreign doctor. In general I felt that this was true since the patients usually spoke freely and seemed relaxed. I also noticed that when the Kenyan staff at the clinic talked with the patients, they acted in the same way as with me during the interviews. One thing that neutralized the power imbalance between me and the mostly female patients was that I had my research assistant and translator, a young, female Kenyan, present at all the interviews. The focus was on the patient and my assistant did most of the talking while I tried to keep myself, as far as possible, in the background. However, some patients asked me if I knew about any new drugs, or vaccines that only existed in "my" country, revealing that they sometimes perceived me as a doctor and not as the independent researcher who I intended to be.

I also took notes during the interviews to describe how I experienced the interview session in terms of patient's body language, whether they talked freely or looked stressed and whether or not they responded to the questions in a relaxed way. The notes were helpful later on during data analysis since they made it easier to get a picture of the patient interviewed and helped me to remember the quality of the interview.

When asking patients where they wanted to be interviewed for Study I, all but two preferred their homes. This was an opportunity for us to gain more insight into the living conditions of the patients. It took some time to adjust to the extremely harsh living conditions under which these people existed. The absence of light in most people's homes made it hard to take notes, for example. The corrugated roof in the houses of mud where the patients were living increased the temperature extensively and made the interview situation challenging and exhausting. Yet, I interpreted the hospitality of the patients as a sign of me being accepted and not being perceived as a threat.

Working with a translator

The best method is always to perform an interview in your own language. Working with a translator has obvious drawbacks and challenges and it is crucial to establish a close relation and to be clear about the working process. The patients interviewed in Kibera all understood English

and could also express themselves, at least on a basic level, in English. Their second language was Swahili, most often spoken more freely, and also used by the translator assisting the author in all interview studies. Apart from English and Swahili, there are about 40 different local languages in Kenya. In only two of the interviews (Study IV) did the patients ask to be interviewed in their native language. We then asked a health staff person to perform these particular translations.

The interview process was thoroughly developed in a close dialogue between the author and the translator. We found that the best way of performing the interviews was that the author asked the question in English. When the respondent was comfortable in elaborating in English the interview could continue in English. If not, the translator translated to Swahili and then probed further with some follow up questions. After a couple of minutes the translator summarized what had been said to the author, who was then able to ask follow up questions. And so it went on, back and forth.

Triangulation of methods and persons

> *"Because each method reveals different aspects of empirical reality, multiple methods of data collection and analysis provide more grist for the research mill."*
> (Patton, 1999)

Triangulation means looking at a research question from different angles in order to reduce systematic bias in data[224]. It is, according to Patton (1999), the best way to perform research but also an expensive way [224]. We used several types of triangulation when performing our studies in the Kibera to look at adherence to ART from different perspectives.

Triangulation of methods: One goal of triangulation is to look for consistencies using different methods [224]. We used different methods to study adherence and drop-out in this thesis. Both qualitative and quantitative, prospective and retrospective methods were used. Qualitative and quantitative methods can complement each other, casting light on the same phenomenon (adherence/drop-out). Also different interview methodologies were used: key informant interviews (situation analysis, Study IV), focus group discussions (Study IV), assisted questionnaire interviews (Study V) and semi-structured interviews (Study I, IV).

Triangulation of objects/data sources: Triangulation of data sources means looking at a phenomenon from different perspectives. In our case we interviewed both staff (social workers, head of clinic, clinical officers, pharmacists, interns, nutritionists), peers and patients about reasons for discontinuing ART (Study IV). Also, when preparing question guides (Study I, IV) and questionnaires (Study II, V) we discussed extensively with and got feedback from social workers, head of clinic, clinical officers and pharmacists.

Researcher/ investigator triangulation: Using different observers/researchers in performing research provides an opportunity to compare findings and to check for interpretive bias [224]. The interviews in Studies I and IV were performed by the author and one research assistant. This gave us the opportunity to compare our impressions and findings. In the analyses of data all co-authors were involved in the process giving their input on the findings and the interpretation of data. The categories and themes from the qualitative interview studies were changed and rephrased a

number of times until consensus was reached in the group. In all phases of the studies the staff from the AMREF clinic were highly involved, giving feedback and suggestions on question guides, questionnaires and formulating consent forms. Additionally the whole research team from Sweden met with staff at the clinic and the responsible researchers from the AMREF head office for two whole-day seminars in Nairobi to discuss and interpret preliminary findings.

Credibility

Credibility in qualitative research refers to how well the data and the analysis reflect the intent of the study [195]. For studies I and IV we chose interview methodologies in order to gain a deeper answers to the research questions (uptake and drop-out) and to be able to freely explore these issues. We also interviewed patients who varied by sex, age, religion, education and living area in order to get broad answers to our research questions. For the analysis, we chose latent content analysis since we wanted to understand the underlying meaning of the texts. In the end, our results, as demonstrated by the categories in study I and IV, might have been more manifest, but the intention was to use latent analysis. For example, in study I we initially defined themes of a more abstract, and latent, character but later took these away and presented only the categories (which are presented in the results of study I and IV) in the final draft.

Generalizability

It may be difficult to generalize our findings from Kibera to all other slums in SSA. An urban slum is a very complex, dynamic environment that changes constantly in set-up and population. Different slums have different set-ups, like in Soweto, South Africa, where houses are better than in Kibera and there is a well-functioning infrastructure. Also, in qualitative research the question about generalizability is not of importance. Rather, the patient's views have to be set into the context of that particular urban slum, which is a very specific environment to live in. From a health system perspective the longitudinal analyses of drop-out rates and the standardized collection of adherence data, allow for comparisons with performance in other similarly challenged health systems. When interviewing patients for Studies I and IV we tried to include patients with different backgrounds; sex, age, ethnic group, religion and place of residence in Kibera in order to at least be able to generalize the results to other HIV patients in Kibera. Particularly in Study I we also put a lot of effort into trying to cover all the different areas in the Kibera slum.

Ethical dilemmas in the research process

There were many discussions before starting Study I about how to get in contact with the patients who had not shown up for ARV treatment. Much of what was learned in Study I about the ethical dilemmas in performing research in the Kibera slum was applied in the succeeding studies (Study II-V).

The patients in Study I had been tested at the MSF clinic, were considered eligible, but had not shown up for treatment. This could have been interpreted as indicating that they did not want to have anything to do with MSF and to approach the patients again could have been ethically questionable. Therefore the decision how to approach the patients was extensively discussed both with the MSF staff and within our research team prior to study start:

- People were contacted by the community health worker in such a way that nobody around them, neighbours or family members, would understand that the person was HIV-infected.
- The interviews to be done were totally confidential. The MSF staff could not identify the persons who were interviewed based on the transcribed interview material.
- We always emphasized to patients that no matter what information emerged from the interviews, this would not have any impact of possible future treatment.
- Precautions were taken so that nobody would be able to witness or hear the interviews that were taking place in a location chosen by the patients themselves.

CONCLUSIONS

- The main reasons for HIV infected individuals in the Kibera slum turning down the offer of free ART were the lack of food and the resulting fear of taking the medication on an empty stomach. This reveals the impact of poverty and illiteracy on ART uptake in this context (Study I).

- At long-term follow-up, between one quarter and one third of all patients could be defined as non-adherent to ART at a level where they would risk symptom relapse or resistance development (Study III, V).

- Absolute poverty, lower education, lack of a treatment buddy and non-disclosure to family members were all risk factors of low adherence to ART (Study V).

- The civil strife resulting from the elections in January 2008 made three times as many patients on ART (42%) miss their drug refill appointments compared to the previous year. This demonstrates the vulnerability of ART provision in a politically volatile urban slum in Sub-Saharan Africa (Study II).

- About 1 in 4 patients dropped out from the ART programme for more than 90 days (Study III, V).

- Not being a resident in Kibera and having a treatment buddy were associated with a lower risk of drop-out from the ART programme (Study III, V).

- Patients had a stronger belief in traditional medicine than in biomedical medicine and religious beliefs were also found to compete with ART. Patients dropped-out from ART following a trigger event often associated with traditional medicine and religious practices (Study IV).

- The competition for HIV patients and lack of referral between different externally-financed providers undermines retention in care and adequate follow-up of patients on ART.

- An open, non-judgemental staff attitude towards discussing potential and expected challenges related to food shortages, traditional medicine, religion, stigma and non-disclosure could reduce the risk for low adherence and drop-out from ART programmes.

IMPLICATIONS OF FINDINGS/ FUTURE PERSPECTIVE

In order to scale-up access to ART and ensure long-term sustainability to these programmes in urban Africa, it is important to invest in poverty reduction strategies for people living in the slums. Thus, food subsidies to the poorest may be needed as well as more oral information about the possible consequences of taking drugs on an empty stomach compared to not taking them at all, which should be part of basic pre-ART counselling. Stigma is a barrier to uptake of ART and health care providers must go beyond the traditional healthcare boundaries and raise community awareness e.g. through talks at local churches and schools. Health care to PLHIV should be expanded and go beyond the traditional (paternalistic) patient-doctor encounter. Patients, relatives and communities could take over some of the tasks currently carried out by health care workers, such as treatment education, early referral mechanisms and/or defaulter tracing. Feasible tools to assess readiness for HIV treatment in the sub-Saharan context are also needed.

A high proportion of patients were classsified as non-adherent to ART at a level where they would risk symptom relapse or resistance development. These issues must be addressed using context-specific interventions, both at community and individual level. Patients should, for example, be strongly encouraged to have a treatment buddy. More home visits by community workers could be performed to encourage patients to go for drug refills on time and to emphasize the importance of adherence. Early identification of vulnerable patients with low adherence should be done through intensified but non-judgemental discussions around self-reported adherence and challenges to live up to treatment recommendations in order to specifically target these patients with supportive interventions like, e.g., electronic alarms, home visits and telephone calls. Fighting stigma in the community is of the essence since this is a powerful barrier to adherence. If policymakers and funders are serious about making life-long ART available for patients in sub-Saharan Africa, it is important to avoid competition between providers and to reduce the short-term funding strategies seen in this area.

Discontinuation of ART could be reduced if ART providers become better at acknowledging and addressing the importance of religious issues and traditional medicine in the lives of patients in resource-poor settings where stigma, poverty and lack of food and social support are key elements in the lives of HIV patients. An open, non-judgmental, discussion with staff around patients' beliefs and practices as part of standard counselling would make patients more comfortable to discuss doubts regarding ART. It is furthermore important to perform studies tracing patients that are LTFU and to better monitor to what extent these patients are still in programs at other health facilities. Talking to religious leaders and traditional healers to understand their views of ART and to seek their help in supporting HIV patients on ART would be one important strategy towards reducing the risk of programme drop-out. Peer groups could also be used to prepare patients for common trigger events that have caused others to discontinue treatment.

A back-up plan is needed to handle situations like civil strife in turbulent, multi-ethnic, poor settings such as urban slums in Africa. Pre-agreements to coordinate service provision or refer patients between providers in case of crisis are necessary precautions in similar areas since treatment interruption may cause irreversible harm to patients on chronic treatment. During times of civil strife it is important to make both the local government and external donors feel accountable not only for providing drugs but also for improving the living conditions and the social support for the patients living in the slum.

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Appendix 1
Question guide, Study I

Question guide Kibera MSF Study

As mentioned previously (consent form), you have been asked to participate in a study to better understand why patients who have been offered HIV treatment choose not to take this treatment. We would like to find out the reasons why patients do not accept ARV-treatment and how, if possible, we can improve our services. This will benefit patients so that more patients start a treatment against HIV.

This study will be run by researchers from the Karolinska institute of Stockholm in collaboration with Medecins Sans Frontieres and the Ministry of Health of Kenya.
This study and your participation will help to guide us on better treating the patients with HIV but you can withdraw at anytime during the interview.

- Can you first tell us about your family? Are you married?
- Do you have any children? If so, how many? Where do they live?
- How many people live in your household?

Can you tell us about HIV, how it all started for you?
- When and how did you find out that you where HIV-positive?
- How did you react when you tested positive?
- Do you know if any other family member is HIV-positive? How did you find it out?
- Has anyone in the family died of HIV/AIDS?

You have been offered ART but not taken it. Can you tell us about this?
- What are your thoughts about side effects from treatment?
- What do you think will happen with a HIV-positive person that doesn't take medication?
- What do you find is the biggest obstacle against taking these drugs regularly?
- What do you think about a "treatment-assistant" or a "treatment-buddy"?
- Do you think it is possible to have a lifelong treatment without disclosure?
- Have you visited a traditional doctor after being tested positive?
- If yes, what recommendations did you get from your traditional healer?
- What do you think about life-long treatment? How does it affect you?

Have you told anyone about your disease?
- Do you know anyone living with HIV?
- What do you think would happen if you told more people about your disease?
- What do you think about telling your sex-partner(s) about you being HIV-positive?

How did you get in contact with MSF?
- Can you tell us about the meeting with the staff at MSF? How were you received?
- What did you think about the VCT-session at MSF?
- What did you think about the follow-up/clinical visit?
- What did you think about the time between assessment and treatment-start? Too long/short?
- What do you think about the opening hours of the clinics MSF-clinics?
- What language(s) do you speak?
- What do you do for a living?
- Are working conditions hampering you from starting/taking treatment?
- Can you read?

Thank you so much for participating in this interview!

Appendix 2.
Question guide, Study IV

AMREF African Medical and Research Foundation

Karolinska Institutet

Question guide: Reasons for defaulting from ARV

Patient: **Sex:**_____ **Age:** _____

Interviewed at:_____ **Defaulted from:**_____

Informed consent: **Date:**

1. Theme: Adherence to ARV

- Are you taking any HIV-medicine at present?
- Have you ever stopped taking your ARV? If so, for how long?
- What was the main reason for this?

  _____
- **Apart from ARV, do you know of any other way(s) of treating HIV?**

  _____

2. Theme: TM

- Do you know anyone, or have you yourself ever considered traditional medicine?
- Where do you get that kind of treatment?
- Have you taken this treatment at the same time as ART?
- What kind of positive and negative effects have you experienced with TM?
- Do you know of any other TM (scarring, urine-drinking etc)
- Cost of treatment?
- Side-effects?
- Would you recommend others to take the same treatment?

3. Theme: Healing

- What kind of spiritual support do you have?
- Where do you get this?
- In what way does it help you?
- What made you choose this specific treatment?
- Who is supporting you in this specific treatment?
- What are your thoughts about getting cured through healing?

Appendix 3.

Karnofsky's performance scale used at the AMREF clinic at screening and follow-up visits, Study III.

Karnofsky %	Patient status
100%	Normal, no complaints
90%	Able to carry on normal activities with minor signs & symptoms
80%	Normal activity with effort
70%	Cares for self, but unable to carry out normal activity or do active work
60%	Requiresoccasiona1 assistance, but able to care for most of their needs
50%	Requires considerable assistance and frequent medical care
40%	Disabled; requires special care and assistance
30%	Severely disabled; hospitalization indicated but death not imminent
20%	Very sick; hospitalization necessary; active support treatment needed
10%	Moribund

Appendix 4
Questionnaire, study II

Questionnaire: Health staffs' perceptions about the current situation in the Kibera slum, January 2008

Please fill in this form on the computer where there is space, then save it on your computer of flash-disc and leave it to Dr Waweru.

1. According to you, which are the reasons for patients not showing up for scheduled appointments during the period of violence after the elections?

2. Have you had problems coming to the clinic yourself? If so, why?

3. Has there been a shortage of drugs or any other materiel at the clinic this past month?

4. If you have met patients from other organisations, have they been supplied with drugs from Amref?

5. Do you know if AMREF patients have gotten drugs from other organisations during this period if they have asked for it?

6. Is there anything else you would like to add regarding the present situation in Kibera that might affect the patients' ability to get their ARV?

Questions directed to community health workers:

7. ***Have you been able to trace the missing patients? If not, please explain why.***

8. ***Have you had the possibility to attempt to trace the missing patients? If not, please explain why.***

Thank you for your participation!

Appendix 5

Baseline questionnaire, Study V

Baseline Questionnaire

Date/Tarehe:_____ **OP/No**/La :_____

_____

I hereby confirm that the conditions of this study have been read to me and I accept to participate. Nadhihiri ya Kwamba nimeleezewa Kuhuso utafiti huo na nimekubali Kushiriki.

The answers you give on this form will be used to plan ways to help other people who must take pills on a difficult schedule. Please do the best you can to answer all the questions. If you do not wish to answer a question, please draw a line through it. If you do not know how to answer a question, ask your interviewer for help. Thank you for helping in this important study/ Majibu utakazo zitoa katika fomu hii itatumiwa kwa kupanga mbinu za kuwasaidia watu ambao wanameza dawa kwa mpangilio ngumu. Tafadhali jaribu uwezavyo kuyajibu maswali yote. Usipotaka kuijibu swali lolote, chora laini uikate. Usipojua jinsi ya kuijibu swali lolote, muulize mhudumu akusaidie. Twakushukuru kwa kusaidia katika utafiti huu muhimu

Please check *one* of the options below/ Chagua moja kati ya zilizotolewa hapo chini

A. Sociodemographic characteristics

1. Sex/Jinsia

1. Female/Mke ☐
2. Male/Mume ☐

2. Age/Umri _____

3. Which ethnic group do you belong to/ Wewe ni kabila gani?

1. Luo/Mjaluo ☐
2. Kisii/Mkisii ☐
3. Kamba/Mkamba ☐
4. Kikuyu/Mkikuyi ☐
5. Maasai/Maasai ☐
6. Luhya/Mluhya ☐
7. Nubien/Mnubi ☐
8. Somali/Msomali ☐
9. Other/Ingine ☐ **Please specify**/Tafadhali dhihiri:_____

4. Which religion do you belong to/Unashiriki dini gani?

1. Protestant/Anglikana ☐
2. Catholic/Katoliki ☐
3. Muslim/Islamu ☐
4. Other/Ingine ☐ **Please pecify**/Tafadhali dhihiri:_____

5. What is the highest level of education you have achieved/ Ni kiwango kipi cha juu cha elimu uliyo nao?

1. Never been to school/Sijawahi kwenda shule ☐
2. Primary school/Shule ya msingi ☐
3. Secondary school/Shule ya upili ☐
4. Tertiary/vocational school/Shule ya ufundi ☐
5. University/Chuo kikuu ☐

6. What is your present occupation/Unafanya kazi aina gani?

1. Employed/Kuandikwa ☐
2. Self-employed/Kujiandika binafsi(Biashara) ☐
3. Unemployed/Kukosa ajira ☐
4. Casual labour/Kazi ya mkoNo/La ☐
5. Other /Ingine ☐**Please specify**/ Tafadhali dhihiri:_____

7. How much do you earn in a month/Unalipwa hela ngapi kila mwezi?

1. < Ksh 1000 ☐
2. Ksh 1000-5000 ☐
3. Ksh 5000-10,000 ☐
4. > Ksh 10,000 ☐
5. Not certain/Sina uhakika ☐

8. What is your marital status/ Jinsia yako ya ndoa ni upi?

1. Married to one partner/Umeolewa kwa mtu mmoja ☐
2. Married to more than one partner/Umeolewa kwa zaidi ya mtu mmoja ☐
3. Widow/widower/Mjane ☐
4. Single/Hujaolewa ☐
5. Divorced/separated/Umepewa talaka ☐

9a. How many people do you reside with, excluding yourself/Unaishi na watu wangapi, bila kujihesabu wewe mwenyewe?

1. 0 ☐
2. 1 ☐
3. 2-3 ☐
4. 4-5 ☐
5. ≥6 ☐

9b. What is the nature of relationship of those you reside with/ Ni uhusiaNo/La gani ulioko kati yako na wale unaoishi nao?

(You may check more than one option/Unaweza kuchagua zaidi ya moja**)**

1. Wife/husband/partner/Mke/Mume/Mpenzi ☐
2. Children/Watoto ☐
3. Friends/Marafiki ☐
4. Relatives/Jamaa ☐
5. Other/Ingine ☐**Please specify**/Tafadhali dhihiri: ___

10. How many biological children do you have/Unao watoto wangapi ulio wazaa?

1. 0 ☐
2. 1 ☐
3. 2-3 ☐
4. 4-5 ☐
5. 6-7 ☐
6. ≥8 ☐

11. How many people are you supporting financially (exclude self)/Ni watu wangapi unaowakimu kifedha (bila kujihesabu)?

1. 0 ☐
2. 1 ☐
3. 2-3 ☐
4. 4-5 ☐
5. 6-7 ☐
6. ≥8 ☐

12. Are you living in Kibera/Unaishi Kibera?

1. Yes/Ndio ☐
2. No/La ☐

If response is No, Please specify and skip next question/ Kama jibu ni La, tafadhali dhihiri kisha uruke swali linalofuata

13. How long have you been living in Kibera/ Umeishi Kibera kwa muda gani?

1. 0-2 years/Chini ya miaka miwili ☐
2. 2-5 years/Kati ya miaka miwili na mitaNo/La ☐
3. >5 years/ Zaidi ya miaka taNo/La ☐

14. How long does it take you to reach the clinic from your residence/Wewe huchukua muda wa kiasi gani kufika kliniki ukitoka kwako?

1. Less than 10 minutes/Chini ya dakika kumi ☐
2. 10-30 minutes/Kati ya dakika kumi na nusu saa ☐
3. 31-60 minutes/Kati ya nusu saa na saa moja ☐
4. More than one hour/Zaidi ya saa moja ☐

B. Transmission, ART initiation, social support

1. How long ago did you learn your HIV status/Ni lini ulipogundua hali yako ya HIV?

1. < 6 months ago/chini ya miezi sita iliyopita ☐
2. 6-12 months ago /kati ya miezi sita na kumi na mbili iliyopita ☐
3. 1-2 years ago/kati ya mwaka mmoja na miwili iliyopita ☐
4. >2 years ago/zaidi ya miaka miwili iliyopita ☐

2a. Have you disclosed your HIV status to anyone/ Umemwambia mtu yeyote kuhusu hali yako ya HIV?

1. Yes/Ndio ☐
2. No/La ☐

2b. If Yes, please state who/Kama ndio, tafadhali dhihiri ni nani:
(You may check more than one option/Unaweza kuchagua zaidi ya moja**)**

1. Partner/Wife/Husband/Mpenzi/Bibi/Bwana ☐
2. Friend/Rafiki ☐
3. Relative/Jamaa ☐
4. Other/Ingine ☐

Please specify/Tafadhali dhihiri: _____

3. How long have you been on ARVs/ Unetumia madawa ya ARV kwa muda gani? **(Year/**Mwaka**, month(s)/**Mwezi(Miezi))

_____

4. Where did you get your drugs from in the beginning/ Ulipata dawa zako kutoka wapi mwanzoni?

1. AMREF ☐
2. MSF ☐
3. From a friend/Kwa rafiki ☐
4. Buy from private vendor/Ulinunua kwa muuzaji ☐
5. Other /Ingine ☐

Please specify/Tafadhali dhihiri:

5. Have you ever taken any other medication during your use of ARVs/ Umewahi kutumia dawa zozote zingine wakati unapotumia ARV's? **(You may check more than one option/**Unaweza kuchagua zaidi ya moja**)**

1. Drugs for Opportunistic Infections ☐
2. Herbs/ Madawa ya kiasili ☐
3. Other ARVs from other organizations ☐
4. No/Lane ☐
5. Other/Ingine ☐

Please specify/ Tafadhali dhihiri: _____

6. Have you ever been hospitalized after starting ART/ Umeshawahi kulazwa hospitalini baada ya kuanza kutumia madawa ya ARV?

1. Yes/Ndio ☐
2. No/La ☐

7. Do you have a treatment buddy/Unaye rafiki wa matibabu?

3. Yes/Ndio ☐
4. No/La ☐

8. In general, are you satisfied with the overall support you get from your friends and family members/ Kwa jumla, unaridhika na usaidizi unayo pata kutoka kwa marafiki na jamaa zako?

1. Yes/Ndio ☐
2. No/La ☐

9. Do your friends or family members help you remember to take your medication/ Marafiki na jamaa zako hukusaidia kukumbuka kumeza dawa ?

1. Yes/Ndio ☐
2. No/La ☐

C. Alcohol and other drugs

1. How often have you had a drink containing alcohol – a glass of beer, changaa, karobo, busaa- in the past 30 days?/ Umetumia kinywaji cha pombe - glasi ya beer, changáa, karobo, busaa – kwa jinsi gani siku 30 iliyopita?

1. Daily/Kila siku ☐
2. Nearly every day/Karibu kila siku ☐
3. 3 or 4 times a week/Mara tatu au nne kwa wiki ☐
4. Once or twice a week/Mara moja au mbili kwa wiki ☐
5. Two or three times a month/Mara mbili au tatu kwa mwezi ☐
6. Once a month/Mara moja kwa mwezi ☐
7. Never/Sijatumia ☐

If Never, skip question 2

2. When you drank alcohol in the last 30 days, how many glasses did you drink altogether at each occasion/ Ulipokunywa pombe siku thelathini iliyopita, Ulikunywa gilasi ngapi kila wakati? **(One bottle equals two glasses, one container equals 2 glasses/** Chupa moja ni gilasi mbili, bilauri moja ni gilasi mbili)

1. 1-2 glasses per day/Moja au mbili kwa siku ☐
2. 3-4 glasses per day/Tatu au nne kwa siku ☐
3. 5-6 glasses per day/TaNo/La au sita kwa siku ☐
4. 7-8 glasses per day/Saba au nane kwa siku ☐
5. 9-10 glasses per day/Tisa au kumi kwa siku ☐
6. 11-12 glasses per day/Kumi na moja au kumi na mbili kwa siku ☐
7. ≥13 glasses per day/ Zaidi yas kumi na tatu kwa siku ☐

3. Have you used Heroin, Marijuana(Bhang), Cocaine, Miraa, Khat, Kuber or any other drug in the past 30 days/ Umetumia heroine, bangi, cocaine, miraa au madawa mengine ya kulevya kwa siku thelathini iliyopita?

1. Yes/Ndio ☐
2. No/La ☐

If response is Yes, check below/Kama jibu ni ndio, chagua hapo chini

1. Heroin ☐
2. Marijuana/Bangi ☐
3. Cocaine ☐
4. Khat/Miraa ☐
5. Kuber ☐
6. Other/Ingine ☐ **Please specify/**Tafadhali dhihiri:_____

D. Sexuality

1. What is (are)the most likely way(s) that you became infected with HIV/ Ni kwa njia gani ambayo unafikiri uliambukizwa HIV?

Check those that apply/Chagua zile unafikiri

1. Sex with a man who was HIV+/Kufanya mapenzi na mwana mume aliye na HIV ☐
2. Sex with a woman who was HIV+/Kufanya mapenzi na mwana mke aliye na HIV ☐
3. Shared needles with a person who was HIV+/Kutumia sindaNo/La na mtu aliye na HIV ☐
4. Blood transfusion or other medical procedure/ Kupewa damu au matibabu zingine ☐
5. Raped/ Kubakwa ☐
6. From my mother at birth/Kutoka kwa mama wakati wa kujifungua ☐
7. Other/Ingine ☐

   Please specify/ Tafadhali dhihiri:_____

2. How old were you when you first had penetrative sexual intercourse/Ulikuwa na miaka ngapi ulipofanya mapenzi mara ya kwanza? _____

Don't know ☐

3. How many sexual partners have you had sex with in the past 6 months/ Umekuwa na wapenzi wangapi ambao umefanya mapenzi nao katika miezi sita iliyopita?

1. 0/Bila ☐
2. 1/Mmoja ☐
3. 2/Wawili ☐
4. ≥3/Zaidi ya tatu ☐ **If ≥3 please specify** /Zaidi ya tatu tafadhali dhihiri:

_____

4a. Compared with six months ago, how has you desire for sex changed/ Ukilinganisha na miezi sita iliyopita, ni kwa njia gani hamu yako ya kufanya mapenzi imebadilika ?

1. My desire for sex has not changed/Hamu yangu ya kufanya mapenzi haijabadilika ☐
2. My desire for sex has increased/ Hamu yangu ya kufanya mapenzi imezidi ☐
3. My desire for sex has decreased/ Hamu yangu ya kufanya mapenzi imepungua ☐

4b. If not sexually active, please fill in why/ Kama hufanyi mapenzi, tafadhali eleza kwa nini?

1. Not feeling well (physically or mentally)/Mimi ni mgonjwa(kimwili au kiakili) ☐
2. Decreased desire to have sex/Sina hamu ya kufanya mapenzi ☐
3. No partner/Sina mpenzi ☐
4. Other reason/Sababu zingine ☐
   Please specify/ Tafadhali dhihiri:_____

5a. How often do you use condoms when having sexual intercourse/ Wewe hutumia mipira mara ngapi ukifanya mapenzi?

1. Never/Hapana ☐
2. Less than half of the times/Chini ya nusu ya nyakati zote ☐
3. More than half of the times/Zaidi ya nusu ya nyakati zote ☐
4. Always/Kila wakati ☐

(**If response is always, skip next question/**Kama jibu ni kila wakati, ruka swali inayofuata)

5b. There are many reasons for not always using a condom, which of the following apply for you/ Kuna sababu nyingi za kutotumia mpira,kati ya hizi zifuatazo, ipi kinakuzuia?

1. Not always available/ Haipatikani kila wakati ☐
2. Too expensive/Bei ghali ☐
3. Partner refused/Mpenzi alikataa ☐
4. Don't like them/Sizipendi ☐
5. Used other contraceptive/Nilitumia njia ingine ya kupanga uzazi ☐
6. Wanted to get pregnant/make my woman pregnant/Nilitaka kushika au kumpa mke mimba ☐
7. Other /Ingine ☐
   Please specify?Tafadhali dhihiri: _____

6. What are you doing to reduce the risk of HIV transmission/Unafanya nini kusaidia kuzuia usambazaji wa HIV?

1. Use condoms/Kutumia mpira ☐
2. Reduction of number of partners/ Kupunguza idadi ya wapenzi ☐
3. Abstinence/Kutofanya mapenzi ☐
4. Nothing, not a concern/Sifanyi chochote, sio shida yangu ☐
5. Other /Ingine ☐
   Please specify/Tafadhali dhihiri:_____

If you haven't started ART, please skip section *E* and *F* below/ Ikiwa hujaanza matibabu ya ART, ruka sehemu mbili E na F zinazofuatia.

E. Adherence

1. When was the last time you missed taking any of your medications/Ni lini mara ya mwisho ulipokosa kutumia yoyote kati ya matibabu yako? **Check one box**/Chagua moja

1. ☐ Within the past week/katika ya wiki iliyopita
2. ☐ 1-2 weeks ago/kati ya wiki moja hadi mbili iliyopita
3. ☐ 2-4 weeks ago/kati ya wiki mbili hadi nne iliyopita

4. ☐ 1-3 months ago/kati ya mwezi moja hadi tatu iliyopita
5. ☐ More than 3 months ago/zaidi ya miezi tatu iliyopita.
6. ☐ Never skip medications or not applicable. If so, skip the next question

People may miss taking their medications for various reasons. Here is a list of possible reasons why you may have missed taking any medications within the past month. If you have NOT taken any medications within the past month, skip to next question/Watu hukosa kutumia matibabu yao kwa sababu tofauti.Hizi ni baadhi ya sababu zilizokufanya kukosa kutumia matibabu yako katika mwezi uliopita. Kama hujatumia matibabu katika mwezi uliopita, ruka hadi swali inayofuata

2. In the past month, have you ever missed taking your medications because you/ Katika mwezi uliopita, umewahi kukosa kutumia matibabu kwa sababu:
Please check one response for each question/Tafadhali chagua jibu moja kwa kila swali; **Yes or No**/La/Ndio au La

1. Were away from home/Haukuwa nyumbani?
   Yes/Ndio ☐ No/La ☐
2. Were busy with other things/Ulikuwa na shuguli zingine?
   Yes/Ndio ☐ No/La ☐
3. Simply forgot/Ulisahau?
   Yes/Ndio ☐ No/La ☐
4. Had too many pills to take/Ulikuwa na tembe nyingi za kumeza?
   Yes/Ndio ☐ No/La ☐
5. Wanted to avoid side effects/Ulitaka kuzuia madhara ya dawa?
   Yes/Ndio ☐ No/La ☐
6. Did not want others to notice you taking medication/Hukutaka wengine wagundue ya kuwa unatumia matibabu?
   Yes/Ndio ☐ No/La ☐
7. Felt like the drug was toxic-harmful/Ulihisi ya kuwa madawa yanakudhuru?
   Yes/Ndio ☐ No/La ☐
8. Fell asleep-slept through dose time/Ulilala/ulishikwa na usingizi wakati wa kumeza dawa? Yes/Ndio ☐ No/La ☐
9. Felt sick or ill/ Ulijisikia mgonjwa?
   Yes/Ndio ☐ No/La ☐
10. Felt depressed-overwhelmed/Ulikuwa na mawazo mengi?
    Yes/Ndio ☐ No/La ☐
11. Had problem taking pills at specified times (with meals, on empty stomach, etc.)/ Ulikuwa na shida kuzimeza wakati uliosisitizwa (kwa mfano na chakula, kwa tumbo bure, na kadhalika)?
    Yes/Ndio ☐ No/La ☐
12. Ran out of pills/Uliishiwa na madawa?
    Yes/Ndio ☐ No/La ☐
13. Felt good and did not need to take the drugs/Ulikuwa ukisikia vizuri na hukuona haja ya kumeza dawa?
    Yes/Ndio ☐ No/La ☐
14. Took traditional medicine instead/Ulitumia dawa za kienyeji badala?
    Yes/Ndio ☐ No/La ☐
15. My religion didn't allow me to take the pills/Dini yako haikuruhusu utumie dawa?
    Yes/Ndio ☐ No/La ☐

F. The following questions ask about symptoms you might have had during the past four weeks/ Maswali yafuatayo yanauliza juu ya dalili ulizokuwa nazo majuma manne yaliyopita. **Please check (Yes/**Ndio **or No/**La**) if you have had any or several of these symptoms.** Tafadhali chagua ndio au la ikiwa umepata moja au zaidi ya dalili hizi

1. Fatigue or loss of energy/ Uchovu au kukosa nguvu?
   Yes/Ndio ☐ No/La ☐
2. Fevers, chills or sweats/Joto, baridi au jasho?
   Yes/Ndio ☐ No/La ☐
3. Feeling dizzy or light-headed/ Kizunguzungu?
   Yes/Ndio ☐ No/La ☐
4. Pain, numbness or tingling in the hands or feet/Uchungu au kuganda kwa miguu au mikono?
   Yes/Ndio ☐ No/La ☐
5. Trouble remembering/Shida kwa kukumbuka?
   Yes/Ndio ☐ No/La ☐
6. Nausea or vomiting/Kichefuchefu au kutapika?
   Yes/Ndio ☐ No/La ☐
7. Diarrhoea or loose bowel movements/Kuendesha au kusokotwa kwa tumbo?
   Yes/Ndio ☐ No/La ☐
8. Felt sad, down or depressed/Huzuni, unyonge au mawazo?
   Yes/Ndio ☐ No/La ☐
9. Felt nervous or anxious/ Kuwa na wasi wasi au matarajio
   Yes/Ndio ☐ No/La ☐
10. Difficulty falling or staying asleep/Shida kupata usingizi au kulala?
    Yes/Ndio ☐ No/La ☐
11. Skin problems, such as rash, dryness or itching/Shida ya ngozi, upele, kukauka au kuwasha?
    Yes/Ndio ☐ No/La ☐
12. Cough or trouble catching your breath/Kukohoa au kukosa pumzi?
    Yes/Ndio ☐ No/La ☐
13. Headache/Kuumwa kwa kichwa?
    Yes/Ndio ☐ No/La ☐
14. Loss of appetite or a change in the taste of food/Kukosa hamu ya kula au ?
    Yes/Ndio ☐ No/La ☐
15. Bloating, pain or gas in your stomach/ Hewa nyingi kwa tumbo?
    Yes/Ndio ☐ No/La ☐
16. Muscle aches or joint pain/Uchungu wa misuli au viungo?
    Yes/Ndio ☐ No/La ☐
17. Problems with having sex, such as loss of interest or lack of satisfaction/ Shida ya kufanya mapenzi kama kukosa hamu au kutoridhika?
    Yes/Ndio ☐ No/La ☐
18. Changes in the way your body looks, such as fat deposits or weight gain/Mabadiliko kweny jinsia ya mwili kama mafuta mengi mwilini au kunona?
    Yes/Ndio ☐ No/La ☐
19. Problems with weight loss or wasting/Shida ya kupunguka kwa uzito au kukonda zaidi?
    Yes/Ndio ☐ No/La ☐
20. Hair loss or changes in the way your hair looks/Kukatika kwa nywele au kubadilika kwa jinsia ya nywele?
    Yes/Ndio ☐ No/La ☐

Thank you so much for your participation/ Ahsante kwa kushiriki!

Appendix 6

Follow-up questionnaire, Study V

AMREF African Medical and Research Foundation

Karolinska Institutet

Follow Up Questionnaire

Date/Tarehe:_____ **OP**/No :_____

_____

I hereby confirm that the conditions of this study have been read to me and I accept to participate. Nadhihiri ya Kwamba nimeleezewa Kuhuso utafiti huo na nimekubali Kushiriki.

THIS PAGE IS TO BE COMPLETED BY THE PATIENT AND STUDY PERSONNEL TOGETHER

You are currently taking the following anti HIV-drugs (ARV) at the frequency and doses listed/ Hivi sasa unatumia matibabu ya ARV zifuatazo wakati na tembe zifuatazo :
(If you don't know the name of your pill, please fill in the colour "blue pill" or similar/Kama huijui jina la tembe, tafadhali tumia rangi "tembe samawati")

Drug Name/Dose Jina la tembe	**# Pills Each Time** **(Pills Each Dose)** Idadi ya tembe kila wakati	**# Times Per Day** **(Doses Per Day)** Mara ngapi kwa siku

The answers you give on this form will be used to plan ways to help other people who must take pills on a difficult schedule. Please do the best you can to answer all the questions. If you do not wish to answer a question, please draw a line through it. If you do not know how to answer a question, ask your interviewer for help. Thank you for helping in this important study/ Majibu utakazo zitoa katika fomu hii itatumiwa kwa kupanga mbinu za kuwasaidia watu ambao wanameza dawa kwa mpangilio ngumu. Tafadhali jaribu uwezavyo kuyajibu maswali yote. Usipotaka kuijibu swali lolote, chora laini uikate. Usipojua jinsi ya kuijibu swali lolote, muulize mhudumu akusaidie. Twakushukuru kwa kusaidia katika utafiti huu muhimu

The next section of the questionnaire asks about your HIV medications that you took over the last four days/ Sehemu inayofuata inauliza juu ya madawa ya HIV ulizozitumia siku nne zilizopita.

Most people with HIV have many pills to take at different times during the day/ Watu wengi walio na HIV huwa na madawa mengi za kumeza wakati tofauti katika siku.
Many people find it hard to always remember taking their pills/ Watu wengi huwa na ugumu wa kukumbuka kumeza madawa:

- **Some people get busy and forget to carry their pills with them**/ Watu wengine wanazo shughuli nyingi hadi wanasahau kubeba madawa wanako kwenda.
- **Some people find it hard to take their pills according to all the instructions, such as "with meals," or "on an empty stomach," "every 8 hours," "with plenty of fluids./** Watu wengine wanaona ugumu wa kutumia madawa kulingana na maagizo kwa mfani "na chakula" au "kwa tumbo bure", baada ya kila saa nane" na "vinywaji vingi."
- **Some people decide to skip doses to avoid side effects or to just not be taking pills that day/** Watu wwengine huamua tu kutomeza madawa ili kuepuka madhara au kukataa tu hiyo siku.

We need to understand how people with HIV are really managing their medicines/ Tungependa kuelewa jinsi watu walio na HIV wanavyodhibiti matibabu yao. **Please tell us what you are actually doing/** Tafadhali tuambia haswa ni nini unayofanya. **Don't worry about telling us that you don't take all your pills**/ Usijali kutuambia ya kuwa hutumii madawa yako yote. **We need to know what is really happening, not what you think we "want to hear."**/ Tungependa kujua ni nini hawsa kinachoendelea sio kile unafikiri tungependa kusikia.

1. The next section of the questionnaire asks about the HIV medications that you may have missed taking over the last four days/ Sehemu inayofuata inauliza juu ya madawa ya HIV ambazo ulikosa kumeza siku nne zilizopita**. Please complete the following table by filling in the boxes below/** Tafadhali jaza nafasi ulizopewa hapo chini.

IF YOU TOOK ONLY A PORTION OF A DOSE ON ONE OR MORE OF THESE DAYS, PLEASE REPORT THE DOSE(S) AS BEING MISSED. Ulipomeza dawa zozote bila ya kufuatilia maagizo, tafadhali sema ya kuwa hukumeza vilivyo

Step 1	HOW MANY DOSES DID YOU **MISS…**

Names of your anti HIV-drugs/ Majina ya madawa ya kuzuia HIV	**Step 2** **Yesterday**/Jana	**Step 3** **Day before Yesterday**/Juzi (**2 days ago**/siku mbili iliyopita)	**Step 4** **3 days ago**/ Siku tatu zilizopita	**Step 5** **4 days ago/** Siku nne zilizopita
	☐ doses	☐ doses	☐ doses	☐ doses
	☐ doses	☐ doses	☐ doses	☐ doses
	☐ doses	☐ doses	☐ doses	☐ doses
	☐ doses	☐ doses	☐ doses	☐ doses
	☐ doses	☐ doses	☐ doses	☐ doses
	☐ doses	☐ doses	☐ doses	☐ doses
	☐ doses	☐ doses	☐ doses	☐ doses

2. During the past 4 days, on <u>how many days</u> have you missed taking <u>all your doses/</u> <u>Katika siku nne iliyopita,kwa siku ngapi umekosa kutumia dawa zako zote</u>?

(If you took only a portion of a dose on one or more of these days, please report the dose(s) as being missed/ Ikiwa ulitumia tu sehemu ya dawa kwa siku moja au nyingi, tafadhali ripoti kwamba hukutumia dawa.)

☐ None/ La
☐ One day/Siku moja
☐ Two days/Siku mbili
☐ Three days/Siku tatu
☐ Four days/Siku nne

3. Most anti-HIV medications need to be taken on a schedule, such as "2 times a day" or "3 times a day" or "every 8 hours." How closely did you follow your specific schedule over the last four days/ Madawa mengi ya kuzuia HIV zinahitaji kutumiwa kwa mpangilio kwa mfano "mara mbili kwa siku" au "baada ya kila saa nane". Ulifwataje mpangilio wako kwa uhakika katika siku nne zilizopita?

Never/ La hasha ☐
Some Of The Time/ Saa zingine ☐
About Half Of The Time/ Nusu ya muda wote ☐
Most Of The Time/ Karibu muda wote ☐
All Of The Time/ Saa zote ☐

4a. Do any of your anti-HIV medications have special instructions, such as "take with food" or "on an empty stomach" or "with plenty of fluids?/ Yoyote kati ya madawa yako ya kuzuia HIV ina maagizo ya kipekee kwa mfano "tumia na chakula", au "kwenye tumbo bure" au "na vinywaji vingi"? "

Yes/Ndio ☐
No/La ☐

4b. If Yes/, how often did you follow those special instructions over the last four days/ Kama ndio, ni mara ngapi ulifuata maagizo haya ya kipekee kwa muda wa siku nne iliyopita?

Never/ La hasha ☐
Some Of The Time/ Saa zingine ☐
About Half Of The Time/ Nusu ya muda wote ☐
Most Of The Time/ Karibu muda wote ☐
All Of The Time/ Saa zote ☐

5. Some people find that they forget to take their pills on the weekend days/ Watu wengine hupata kama wamesahau kumeza dawa juma mosi na juma pili. **Did you miss any of your anti-HIV medications last weekend— last Saturday or Sunday/** Ulikosa kumeza yoyote kati ya madawa yako ya kuzuia HIV juma mosi au juma pili iliyopita?

Yes/Ndio ☐
No/La ☐

6. **When was the last time you missed taking any of your medications/** Ni lini mara yako ya mwisho kusahau kumeza dawa yako yoyote? **Check one box**/Chagua moja

1. ☐ Within the past week/katika ya wiki iliyopita
2. ☐ 1-2 weeks ago/kati ya wiki moja hadi mbili iliyopita
3. ☐ 2-4 weeks ago/kati ya wiki mbili hadi nne iliyopita
4. ☐ 1-3 months ago/kati ya mwezi moja hadi tatu iliyopita
5. ☐ More than 3 months ago/zaidi ya miezi tatu iliyopita.
6. ☐ Never skipped medications or Not applicable. If so, skip the next question

People may miss taking their medications for various reasons. Here is a list of possible reasons why you may have missed taking any medications within the past month/ Watu hukosa kutumia matibabu yao kwa sababu tofauti. Hizi ni baadhi ya sababu zilizokufanya kukosa kutumia matibabu yako katika mwezi uliopita. Kama hujatumia matibabu katika mwezi uliopita, ruka hadi swali inayofuata

7. In the past month, have you ever missed taking your medications because you/ Katika mwezi uliopita, umewahi kukosa kutumia matibabu kwa sababu:
Please check one response for each question/ Tafadhali chagua jibu moja kwa kila swali; **Yes/**Ndio **or No**/La

1. Were away from home/ Haukuwa nyumbani?
   Yes/Ndio ☐ No/La ☐
2. Were busy with other things/Ulikuwa na shuguli zingine?
   Yes/Ndio ☐ No/La ☐
3. Simply forgot/Ulisahau?
   Yes/Ndio ☐ No/La ☐
4. Had too many pills to take/Ulikuwa na tembe nyingi za kumeza?
   Yes/Ndio ☐ No/La ☐
5. Wanted to avoid side effects/ Ulitaka kuzuia madhara ya dawa?
   Yes/Ndio ☐ No/La ☐

6. Did not want others to notice you taking medication/ Hukutaka wengine wagundue ya kuwa unatumia matibabu?
   Yes/Ndio ☐ No/La ☐
7. Felt like the drug was toxic-harmful/Ulihisi ya kuwa madawa yanakudhuru?
   Yes/Ndio ☐ No/La ☐
8. Fell asleep-slept through dose time/Ulilala/ulishikwa na usingizi wakati wa kumeza dawa?
   Yes/Ndio ☐ No/La ☐
9. Felt sick or ill/Ulijisikia mgonjwa?
   Yes/Ndio ☐ No/La ☐
10. Felt depressed-overwhelmed/Ulikuwa na mawazo mengi?
    Yes/Ndio ☐ No/La ☐
11. Had problem taking pills at specified times (with meals, on empty stomach, etc.)/Ulikuwa na shida kuzimeza wakati uliosisitizwa(kwa mfano na chakula, kwa tumbo bure, na kadhalika)?
    Yes/Ndio ☐ No/La ☐
12. Ran out of pills/Uliishiwa na madawa?
    Yes/Ndio ☐ No/La ☐
13. Felt good and did not need to take the drugs/Ulikuwa ukisikia vizuri na haukuona haja ya kumeza dawa?
    Yes/Ndio ☐ No/La ☐
14. Took traditional medicine instead/ Ulitumia dawa za kienyeji badala?
    Yes/Ndio ☐ No/La ☐
15. My religion didn't allow me to take the pills/ Dini yako haikuruhusu utumie dawa?
    Yes/Ndio ☐ No/La ☐

8.The following questions ask about symptoms you might have had during the past four weeks. Please check (Yes/Ndio or No/La) if you have had any of these symptoms

1. Fatigue or loss of energy/Uchovu au kukosa nguvu?
   Yes/Ndio ☐ No/La ☐
2. Fevers, chills or sweats/Joto, baridi au jasho?
   Yes/Ndio ☐ No/La ☐
3. Feeling dizzy or light-headed/ Kizunguzungu?
   Yes/Ndio ☐ No/La ☐
4. Pain, numbness or tingling in the hands or feet/ Uchungu au kuganda kwa miguu au mikono?
   Yes/Ndio ☐ No/La ☐
5. Trouble remembering/ Shida kwa kukumbuka?
   Yes/Ndio ☐ No/La ☐
6. Nausea or vomiting/ Kichefuchefu au kutapika?
   Yes/Ndio ☐ No/La ☐
7. Diarrhoea or loose bowel movements/ Kuendesha au kusokotwa kwa tumbo?
   Yes/Ndio ☐ No/La ☐
8. Felt sad, down or depressed/Huzuni, unyonge au mawazo?
   Yes/Ndio ☐ No/La ☐
9. Felt nervous or anxious/ Kuwa ns wasi wasi au matarajio
   Yes/Ndio ☐ No/La ☐
10. Difficulty falling or staying asleep/ Shida kupata usingizi au kulala?
    Yes/Ndio ☐ No/La ☐

11. Skin problems, such as rash, dryness or itching/Shida ya ngozi, upele, kukauka au kuwasha?

Yes/Ndio ☐ No/La ☐

12. Cough or trouble catching your breath/ Kukohoa au kukosa pumzi?

Yes/Ndio ☐ No/La ☐

13. Headache/ Kuumwa kwa kichwa?

Yes/Ndio ☐ No/La ☐

14. Loss of appetite or a change in the taste of food/ Kukosa hamu ya kula au chakula kubadili ?

Yes/Ndio ☐ No/La ☐

15. Bloating, pain or gas in your stomach/ Hewa nyingi tumboni?

Yes/Ndio ☐ No/La ☐

16. Muscle aches or joint pain/ Uchungu wa misuli au viungo?

Yes/Ndio ☐ No/La ☐

17. Problems with having sex, such as loss of interest or lack of satisfaction/ Shida ya kufanya mapenzi kama kukosa hamu au kutoridhika?

Yes/Ndio ☐ No/La ☐

18. Changes in the way your body looks, such as fat deposits or weight gain/ Mabadiliko kwenye jinsia ya mwili kama mafuta mengi mwilini au kunona?

Yes/Ndio ☐ No/La ☐

19. Problems with weight loss or wasting/ Shida ya kupunguka kwa uzito au kukonda zaidi?

Yes/Ndio ☐ No/La ☐

20. Hair loss or changes in the way your hair looks/ Kukatika kwa nywele au kubadilika kwa jinsia ya nywele?

Yes/Ndio ☐ No/La ☐

Thank you so much for your participation/ Ahsante kwa kushiriki!

Appendix 7.
Commentary in JAIDS, Unge et al (2009)

Comparing Clinic Retention Between Residents and Nonresidents of Kibera, Kenya

Christian Unge, MD, Björn Södergård, PhD,* Anna Mia Ekström, MD, PhD, MPH,* Jane Carter, MBBS, FRCPC,‡ Marjory Waweru, MD,‡ Festus Ilako, MBchB, Mmed,‡ Anders Ragnarsson, BSc, MSc,* Gaetano Marrone, PhD,† and Anna Mia Thorson, MD, PhD, MPH**

We are grateful to Chung et al who, in response to our article, brought forward several interesting issues regarding retention in care and drop-out from antiretroviral treatment (ART) programs in urban slum settings.[1] Our article presented research performed at the African Medical and Research Foundation (AMREF) clinic in Kibera, one of Africa's largest informal settlements, which showed that being a Kibera resident was significantly associated with ART program drop-out. Additionally, the Cox proportional hazard ratio for dropping-out among Kibera residents was 2.45 ($P = 0.05$), as compared with non–Kibera residents (result not presented in the original article). Chung et al did not find that Kibera residents who attended their study clinic at the Coptic Hope Centre had a higher loss to follow-up (Cox proportional hazard ratio: 1.02) than non–Kibera residents, and thus "caution against the conclusion that residing in Kibera or any urban slum is a risk factor for poor retention."

However, there are important differences in terms of geographical location, patient catchment area, and resources that make this comparison difficult. First, the Coptic Hope Centre clinic is located outside Kibera, whereas the AMREF clinic is located right in the centre of Kibera. Second Chung et al argue that: "Some residents are middle class Kenyans with a yearly salary and not necessarily day laborers with low income." The Kibera population has not previously been well described in terms of sociodemographics and in our retrospective study; we lacked valid data on socioeconomic variables. However, our preliminary data from an ongoing prospective cohort study of HIV patients on ART at the AMREF Kibera clinic support our experience that most patients live under extremely poor conditions. Out of 515 ART patients enrolled so far in our prospective study, only 16% are employed, the other 84% are doing casual labor, are unemployed, or self-employed. Further, only 5% of the respondents have higher education (postsecondary school). Hence, our different findings are likely attributable to selection of more motivated and possibly less vulnerable patients from Kibera seeking care at the Coptic Hope Centre.

Secondly, Chung et al speculate that patients dropping-out from the AMREF program might have sought care at a PEPFAR-funded clinic instead; however, the AMREF program at the Kibera clinic likewise receives funding from PEPFAR via CDC). We lack quantitative data on reasons for loss to follow-up, but our qualitative in-depth studies among HIV patients who have dropped out from the ART program in Kibera suggest that aside from death, migration, and the occasional patient changing provider, poverty and lack of food appear to be the major barriers to retention in an ART program in Kibera.[2] The time spent on clinic visits is considered better used to look for job opportunities, and taking ART is not perceived compatible with hunger and an empty stomach. In our forthcoming prospective study we will be able to further analyze determinants of retention in care.

In addition, we used a more conservative definition of drop-out, 90 days, in order not to over estimate drop-out and to account for short-term migration in the mobile population of Kibera. Chung et al used 30 days as the cut-off. The Coptic Hope Centre clinic included only treatment-naive patients from the age of 15 years, whereas we included both treatment-naive and treatment-experienced patients above the age of 18 years. Our results might thus

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From the *Division of International Health, Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden; †Applied Sciences Department, University of Pavia, Italy; and ‡African Medical and Research Foundation, Kenya Country Program, Nairobi, Kenya.

be underestimating the probabilities of drop-out as compared with Chung's study design. It is therefore very difficult to make any formal comparisons between the 2 cohorts.

Third, Chung et al bring up the issue of geographical proximity to the clinic as a problem for retention. Because HIV-related stigma is an important problem in Kenya, people can be deterred from seeking care at specific HIV clinics close to home where they cannot enter anonymously. This is, however, not the case at the AMREF clinic because it is an integrated health care clinic with a general out-patient department where the same staff serves all patients on a first-come, first-served basis, regardless of HIV status. We think that this in fact reduces health-seeking–related stigma at the AMREF clinic, contrary to the beliefs by Chung et al who have performed their studies at the Coptic Hope Centre clinic, which is an infectious diseases clinic. The number of staff, services available, and the opening hours may also differ.

Kibera residents have several treatment options and may change clinics according to needs and preferences. The "competitive" situation this creates between clinics can be counterproductive and indeed increase the risk of drop-out. Our results are valid for the AMREF clinic in Kibera and points at challenges for the health system to retain patients in care, which are specific to a clinic located within an urban informal settlement, where poverty and mobility rates are exceptionally high. Similar problems are still a reality for many ART clinics in high-HIV prevalence, low-income, and urban Sub-Saharan African settings today. It would, therefore, be interesting to look at gains and cost-effectiveness of retention in care in relation to different models of care and add-on services that are offered, which we hope to include in our future studies.

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